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TEACHING EPIDEMIOLOGY IN OCCUPATIONAL HEALTH

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PREFACE

During the 1980s, the National Institute for Occupational Safety and Health (NIOSH) has helped to protect and preserve the health of workers in developing countries. The World Health Organization (WHO) is also dedicated to this end, and through its Programme of Action on Worker's Health has sought to protect and promote the health of working populations throughout the world.

In reaching toward these objectives, NIOSH and WHO have been able to collaborate on several projects. One project has now resulted in this text, A Joint Publication on Teaching Epidemiology in Occupational Safety and Health. This volume focuses on the need to train occupational epidemiologists in the recognition and evaluation of occupational diseases and injuries. It is a training tool that uses the case approach to instruct epidemiolgists. It is with pride that we publish this book of case studies as an aid to both epidemiologists and the many workers who will benefit from their services.

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TEACHING EPIDEMIOLOGY IN OCCUPATIONAL HEALTH

INDEX

SECTION	CONTENT	AUTHOR	YEAR
A	INDEX PREFACE EDITORS AUTHORS MEETING PARTICIPANTS CONTENT OF CASES DISTRIBUTION OF USERS INTRODUCTION		
B	VINYL CHLORIDE AND LUNG CANCER	HENRY FALK RICHARD WAXWEILER CLARK HEATH	1975
		Revised	1983
C	OCCUPATIONAL NEUROLOGICAL DISEASE	PHILIP J. LANDRIGAN	1979
		Revised	1985
D	LUNG CANCER IN CHEMICAL WORKERS	WILLIAM HALPERIN	1979
		Revised	1985
E	URINARY SYMPTOMS IN POLYURETHANE FOAM WORKERS	KATHLEEN KREISS	1983
		Revised	1985
F	GYNAECOMASTIA IN ESTROGEN EXPOSED WORKZRS	J. MALCOLM HARRINGTON	1983
		Revised	1985
G	LEAD AND RENAL ABNORMALITIES	MICHAEL THUN EDWARD BAKER	1983
H	WASHINGTON SURVEILLANCE PROGRAMME ARSENIC EXPERIENCE - A CASE STUDY	SAM MILHAM	1983
		Revised	1985
I	MALE OCCUPATIONAL REPRODUCTIVE DISEASE	M. DONALD WHORTON	1983
J	MESOTHELIOMA IN RAILROAD WORKERS	MARTIN SEPULVEDA	1983
		Revised	1985
K	HYPERSENSITIVITY PNEUMONITIS IN AN OFFICE BUILDING (A new form of occupational lung disease)	MICHAEL HODGSON PHILIP R. MOREY	1983
L	CANCER MORTALITY IN A DIE CASTING AND ELECTROPLATING PLANT	MICHAEL A. SILVERSTEIN	1983
		Revised	1985
M	LEUKAEMIA IN NUCLEAR SHIPYARD WORKERS (Uses and pitfalls of proportional mortality studies)	MICHAEL THUN JAY BEAUMONT	1983
		Revised	1985

N	MINING, SMOKING AND LUNG CANCER (Problems of interaction and quantification of risk)	OLAV AXELSON		1985
O	MORTALITY STUDY TESTING A POSSIBLE ASSOCIATION BETWEEN OCCUPATIONAL EXPOSURE TO FORMALDEHYDE AND CANCER	PIER A. BERTAZZI		1984
		Revised		1985
P	EXPOSURE-RESPONSE; RELATIONSHIP BETWEEN EXPOSURE STYRENE AND CENTRAL NERVOUS FUNCTIONS	SVEN HERNBERG HANNU HARKONEN		1984
		Revised		1985
Q	OCCUPATIONAL ASTHMA DUE TO PLATINUM SALTS	DEAN BAKER		1985
		Revised	Dec	1985
R	PESTICIDE POISONING AMONG ANTIMALARIA WORKERS	J. JEYARATNAM		1985
		Revised	Dec	1985
S	CHRONIC RESPIRATORY DISEASE IN COTTON TEXTILE WORKERS	GAMAL EL-SAMRA		1985
		Revised	Dec	1985
T	FARMER'S LUNG	GU XUE-QI LU PEI-LIAN SHEN YI-E		1985
U	EPIDEMIOLOGY IN PLANNING AND DEVELOPMENT OF OCCUPATIONAL HEALTH SERVICES	M.A. EL BATAWI C. HUSBUMRER		1985

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CONTENT OF CASES

SECTION CONTENT / SUBJECT	B VINYL CHLORIDE	C OCCUPATIONAL NEUROLOGY	D LUNG CANCER	E URINARY SYMPTOMS
STUDY DESIGN				
CROSS SECTIONAL		3		3
COHORT	1		1	
PROPORTIONAL	1		1	
CASE CONTROL				
OTHER CONCEPTUAL ISSUES				
CLUSTER INVESTIGATION	3	3	3	3
SCREENING		1		
SURVEILLANCE			1	
LATENCY	1			
PERSON-YEARS	2			
EXPOSURE ASSESSMENT	1	1		1
CHOOSING A COMPARISON POPULATION			3	
POWER				
DATA ANALYSIS				
SIGNIFICANCE TESTING			2	
CONFIDENCE INTERVALS	1			
STRATIFIED ANALYSIS	1			
REGRESSION				
DEGREE OF DIFFICULTY	2	1	3	1

-- = NOT APPLICABLE; 1 = LOW; 2 = MEDIUM; 3 = HIGH

CONTENT OF CASES

	F GYNAECO-MASTIA	G LEAD/ RENAL	H ARSENIC	I MALE/ REPRODUCTIVE
STUDY DESIGN				
CROSS SECTIONAL	2	3		3
COHORT			1	
PROPORTIONAL			2	
CASE CONTROL				
OTHER CONCEPTUAL ISSUES				
CLUSTER INVESTIGATION	3			3
SCREENING			1	
SURVEILLANCE			2	
LATENCY				
PERSON-YEARS				
EXPOSURE ASSESSMENT	1	1	2	1
CHOOSING A COMPARISON POPULATION				
POWER				
DATA ANALYSIS				
SIGNIFICANCE TESTING		1	1	
CONFIDENCE INTERVALS				
STRATIFIED ANALYSIS				
REGRESSION		1		
DEGREE OF DIFFICULTY	2	3	1	1

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CONTENT OF CASES

	J	K	L	M
	MESOTHELIOMA	HYPERSENSITIVITY	DIE CASTING	NUCLEAR SHIPYARD
STUDY DESIGN				
CROSS SECTIONAL	3	3		
COHORT				1
PROPORTIONAL			3	3
CASE CONTROL				
OTHER CONCEPTUAL ISSUES				
CLUSTER INVESTIGATION	3	3		
SCREENING				
SURVEILLANCE				
LATENCY	1			
PERSON-YEARS				
EXPOSURE ASSESSMENT			1	
CHOOSING A COMPARISON POPULATION				
POWER				
DATA ANALYSIS				
SIGNIFICANCE TESTING			1	
CONFIDENCE INTERVALS			1	1
STRATIFIED ANALYSIS				
REGRESSION				
DEGREE OF DIFFICULTY	1	1	1	1

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CONTENT OF CASES

	N	O	P	Q
	MINING/ SMOKING	FORMALDE-HYDE	STYRENE	OCCUPATIONAL ASTHMA
STUDY DESIGN			2	2
CROSS SECTIONAL				
COHORT	3	3		
PROPORTIONAL				
CASE CONTROL				
OTHER CONCEPTUAL ISSUES				
CLUSTER INVESTIGATION				2
SCREENING			1	2
SURVEILLANCE				
LATENCY	3	3		2
PERSON-YEARS		2		
EXPOSURE ASSESSMENT	3	1	3	1
CHOOSING A COMPARISON POPULATION	3	1	3	
POWER		2		
DATA ANALYSIS				
SIGNIFICANCE TESTING	3	1		
CONFIDENCE INTERVALS	3	2	2	
STRATIFIED ANALYSIS	3			2
REGRESSION			2	
DEGREE OF DIFFICULTY	3	3	3	2

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CONTENT OF CASES

	R PESTICIDE	S RESPIRATORY DISEASE COTTON	T FARMERS LUNG	U EPID IN HEALTH SERVICE
STUDY DESIGN				
CROSS SECTIONAL	3	2	3	3
COHORT				
PROPORTIONAL				2
CASE CONTROL				
OTHER CONCEPTUAL ISSUES				
CLUSTER INVESTIGATION	3			1
SCREENING	1			1
SURVEILLANCE	1	2	2	
LATENCY				
PERSON-YEARS				
EXPOSURE ASSESSMENT	3	1	2	2
CHOOSING A COMPARISON POPULATION		1		
POWER				
DATA ANALYSIS				
SIGNIFICANCE TESTING				2
CONFIDENCE INTERVALS				
STRATIFIED ANALYSIS				2
REGRESSION				
DEGREE OF DIFFICULTY	1	1	1	1

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INTRODUCTION

The recognition and prevention of occupational diseases and injuries relies, in part, on well trained occupational epidemiologists. Skilled public health practicioners are needed to assess and intervene in a wide variety of problems, ranging from occupational health in developing countries, the recognition of new hazards, the development of methods and sound research in new areas such as the reproductive, cardiovascular and psychologic effects of work, the study of multifactorial diseases such as hypertension or low back syndrome, and the quantification of dose-response relationships.

The issue of worker health in developing countries is of particular concern. An urgent need exists for personnel who can recognize, evaluate and prevent occupational problems. The current paucity of information has resulted in occupational health having a low priority in many of these countries, in spite of the fact that occupational diseases are an important concern in industrial and socioeconomic development of these countries. Workers are a major and important sector of the community; they are the bread-winners of families and their health is a major factor in development. Developing countries are now realizing the need for sound occupational health programmes. In order to plan, develop and follow through with appropriate programmes that are relevant to their particular needs, developing countries need to identify the types and magnitude of health problems of their workers using adequate epidemiological methods.

For these reasons, the World Health Organization, in its Programme of Action on Workers' Health (1979), identified occupational epidemiology as a major priority in the training of occupational health personnel from different countries and in the institutional development of occupational health services. Guides have been developed and courses on epidemiology have been organized in various parts of the world.

Under two Cooperative Agreements between the National Institute for Occupational Safety and Health (NIOSH) and the World Health Organization (WHO) in 1981-1984 and 1984-1987, epidemiology has been a prominent part of these Agreements aiming at assisting WHO in the full implementation of the Programme of Action on Workers' Health.

This book is one of the important outputs of NIOSH/WHO cooperation.

Dr William Halperin of NIOSH has, since 1979, been selecting epidemiological studies and collaborating with their authors in adapting these studies and their presentation for teaching purposes. He laid the foundation by developing and using these studies in teaching students in epidemiology at different levels, though mainly postgraduate. The Occupational Health Programme of WHO arranged with NIOSH to widen the scope, increase the number and internationalize this educational material. Guest editors and authors were invited from different parts of the world to an interregional workshop on occupational epidemiology held in Alexandria, Egypt, in November 1984 (see"Participants") and reviewed the available material, added new studies and made editorial suggestions. The Editorial Committee has since then finalized the present text.

This collection of teaching cases is being provided to teachers of occupational epidemiology jointly by the National Institute for Occupational Safety and Health of the United States of America and by the World Health Organization. These cases are intended as practical classroom exercises to supplement lectures on the same material. Similar case studies have proven useful in teaching the concepts of the epidemiology of infectious diseases at the Centers for Disease Control in the USA.

This collection of cases covers a wide range of subject matter and presents a spectrum of difficulty. Some cases demonstrate methods used in the investigation of clusters of cases and acute outbreaks; other cases illustrate methods of chronic disease epidemiology. An outline of the content, including the degree of difficulty of the cases, is provided. In this table, the cases have been grouped into broad categories beginning with cluster investigations and cross-sectional studies, and progressing to retrospective cohort mortality studies, consideration of statistical power, and other methodological issues. Many issues are addressed by more than one case. The instructor may find the table of content of cases of value in selecting those cases that present the desired mix of issues.

The teaching cases are designed to be distributed, read, worked, and discussed by the students part by part. Each part is completed by the class before the next is considered. Instructors are strongly advised to work through the case in this step-wise fashion themselves before attempting to teach it. Involving more advanced students, as assistants to the instructor, offers them an unusual learning experience. Time should be allowed for the distribution of the part, and working the part either alone or in small groups of students.

Each case is accompanied by a set of notes for the instructors. These notes summarize the salient points that the case is intended to illustrate, and provide possible answers to the questions. We urge the instructors, who wish to share these summaries with students, to do so only after the class discussion has been completed, otherwise the process by which the class must develop appropriate and feasible approaches to the problem may be hindered.

The users are advised that many of the introductions to these cases are redundant involving notification of appropriate health authorities of the investigation, division of investigative responsibilities, etc. Once these issues are understood by the class, we urge deleting them from further discussion of the other cases with the same group of students. Many of the investigations discussed in these cases occured in the USA.

Depending on the student population, discussion of professional and bureaucratic interrelationships specific to any particular country may be irrelevant to the needs of the particular students enrolled. We suggest that the cases be modified to include discussions of those issues as they are relevant to the students.

This collection of cases should be considered dynamic. New cases will be added in the future to cover new methodological issues or to replace current cases that may prove problematic in use. We welcome the submission of new cases which will be reviewed for inclusion by the Editorial Committee. We also appreciate your criticisms or proposed revisions. Translations are particularly welcomed. We will provide any new cases or revisions to users of this book, so please be sure to send your name, address, and institutional affiliation, especially if you have received this collection indirectly from another user, rather than directly from NIOSH/USA or WHO. Please send all correspondence to William Halperin M.D., M.P.H., National Institute for Occupational Safety and Health,, 4676 Columbia Parkway, Cincinnati, Ohio, 45226, USA. with a copy to Dr. M. Batawi, World Health Organization, CH-1211 Geneva 27, Switzerland.

Finally, we would like to thank the many authors who have contributed cases to this collection, the numerous reviewers who have made constructive comments, and the many students who have used these cases and offered their suggestions for improvements. The Editorial Committee has responded to these reviews and suggestions by modifying the cases, and accepts responsibility for errors of fact or intent that may have been introduced by us rather than the original authors. We appreciate the work of numerous secretaries who have worked on countless revisions, and especially Janet Graydon.

We believe that epidemiology can contribute to the prevention of occupational disease. We hope that this volume will not only contribute to the education of epidemiologists, but of other professionals as well who might find the epidemiological approach useful in disease prevention. WHO and NIOSH intend to organize international short-term courses using the material of this book with a view to acquiring more experience, so as to improve the contents by taking into account cross-cultural feasibility.

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54

DHHS (NIOSH) Publication No. 87-112

55

VINYL CHLORIDE AND CANCER*

PART 1

In January 1974 the B.F. Goodrich Company notified the United States National Institute for Occupational Safety and Health (NIOSH) that four cases of angiosarcoma of the liver (ASL) had occurred since 1967 in a work force of about 500 long-term workers at a polyvinyl chloride (PVC) production plant in Louisville, Kentucky, USA.

Case number	Age at diagnosis, race, sex	Date of diagnosis	Date of first PVC exposure	Total years of exposure
1	43 white, male	8-67	7-52	15
2	36 white, male	5-70	11-55	13
3	49 white, male	3-73	12-48	16
4	58 white, male	12-73	11-45	28

Although only four cases occurred over a 10-year period (1964-1974), ASL is so rare a tumour that a causal relationship was strongly suspected. The expected incidence of ASL in the general population was derived from the US National Cancer Institute's Third National Cancer Survey (1969-1971) which indicated that only about 27 cases occur per year in the entire population of 200 million in the United States of America.

Question 1

Calculate a crude mortality ratio for ASL in long-term PVC polymerization workers at this plant in the past 10 years. Assume 10 years of observation during which the workers were at risk for developing cancer.

Crude mortality ratio = ____________________

Within just a few days, additional observations were reported which supported the association between vinyl chloride exposure and the development of ASL. First, an Italian study, the preliminary results of which had been presented at the Xth International Cancer Congress at Houston, USA, in 1970, were published in 1971 and had found that rats given long-term inhalation exposure to work-place concentrations of vinyl chloride monomer (VCM) developed not only ASL, but also angiosarcoma at other sites, as well as other malignant tumours (lung, renal). (Viola *et al.*, 1971) Second, detailed clinical and pathological reviews of the four human cases of ASL showed that all four had similar clinical illnesses and similar pathological lesions involving portal hypertension and portal fibrosis in addition to ASL.

Question 2

What further questions are raised both by the finding of four cases of ASL at one plant and by the appearance of ASL and other tumours in rats exposed to VCM?

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* By Henry Falk, Richard Waxweiler, & Clark Heath, 1975. Revised 1985

57

Before proceeding, some background information concerning VCM/PVC is necessary. VCM is a gas ($CH_2 = CHCl$) produced largely through chlorination of ethylene, a byproduct of the petroleum industry. When polymerized, VCM forms PVC, one of four major polymer plastics widely used in the modern world (the other three are polystyrene, polypropylene, and polyethylene). PVC can take various physical forms (liquid, solid, rigid, flexible) depending on chemical additives used (copolymers, plasticizers).

PVC has been produced commercially since the 1930's. Since the Second World War, its production has steadily increased throughout the world, production in the USA in 1974 amounting to 3.5 million tons. As a plastic, it has multiple uses varying from floor tiles and seat covers to toys, water pipes, and tires. VCM until recently was considered a relatively inert gas and as such was widely used as a spray can propellant.

Over one million workers in the USA have some kind of contact with VCM/PVC. These workers can be considered in the following three categories:

1) VCM production. In January 1974, VCM was being produced in 12 different plants in the USA, employing a total of about 1000 workers. The chemical process took place in an essentially closed system of vats and pipes. Workers were directly exposed to VCM only when leaks occur in the system.

2) PVC polymerization. According to the methods used before 1973, the VCM gas, liquified under pressure, was transferred by tank car to polymerization facilities. There were 37 such plants in the USA, as of January 1974, employing a total of about 20 000 workers. In the polymerization process, VCM was introduced into large reactor vessels where polymerization took place under heat and pressure, often in the presence of chemical additives. Following the reaction process, the newly-formed PVC was drained from the vessel. However, residual polymer builds up on the vessel walls, requiring periodic removal, partly by water jet and partly by hand. Cleaning by hand entails workers entering the vessels and spending considerable time in an atmosphere containing increased amounts of VCM. While workers entering reactors are now carefully protected from VCM exposure, in the past little or no protection was thought necessary. Considerable direct exposure to VCM may also occur when workers handle freshly polymerized PVC beyond the reactor vessel. Such fresh PVC may retain substantial amounts of unreacted VCM within its polymer structure, releasing VCM into the air in the process of packing and shipping.

3) PVC fabrication. From polymerization facilities, PVC in various physical forms is shipped to numerous manufacturing concerns throughout the country for fabrication into diverse consumer products. Use of PVC in such fabrication plants varies greatly. Depending upon amounts of PVC used, the ways in which it is used, and the working conditions involved, workers may well be exposed to residual VCM released from PVC plastic. In all, about one million workers are employed in PVC fabrication plants. Many of the plants are small, employing only a handful of workers in each plant.

Question 3

a) Given these facts, what phase of the VCM/PVC industry would be best suited for an epidemiological study of VCM health effects? Why?

b) What is the purpose of conducting further epidemiological studies in this population?

c) What kind of study might be undertaken and why?

d) What criteria would you suggest for selecting groups of workers for study?

PART 2

NIOSH chose to conduct a retrospective cohort mortality study of workers at PVC polymerization plants. The study was designed to follow polymerization workers from the time they entered the industry until the end of December 1973, and to compare observed cause-specific mortality among such workers with that expected based on known USA white male cause-specific mortality rates. Four plants were selected for the study on grounds of length of operation, accessibility of records, and probable ease of followup.

1. B. F. Goodrich, Louisville, Kentucky (where the four original cases had occurred),
2. B. F. Goodrich, Avon Lake, Ohio,
3. General Tire, Ashtabula, Ohio, and
4. Firestone, Pottstown, Pennsylvania.

Since a cohort study itself would take several years to complete, an initial rapid assessment of mortality patterns was undertaken, using available information in medical and insurance records at each plant.

A quicker approach is the proportional mortality study. In a study of proportional mortality rates, the proportion of deaths due to a specific cause (here ASL), in the exposed population, is compared to the proportion expected in a comparison population. In a cohort study, the incidence rate of disease (or the mortality rate from a specific disease) is compared between the exposed and the comparison populations. Proportional mortality studies can be based on available data, while cohort studies require extensive follow-up of cohort members.

From the records available at the selected plants, 144 deaths were identified. This figure includes workers who had died after retirement, as well as workers who had died on the job. All were white males. For each death, the age at death and the date of death were available. Using this information, a proportional mortality analysis was performed to determine if any particular causes of death were unduly represented when compared with what might be expected for white males in the USA as a whole dying at the same ages in the same years. The expected proportions, derived from US mortality rates and adjusted for age and year of death, are shown for specific causes of death in Table I, together with the observed numbers of deaths.

Table I. Proportional mortality ratio

Cause of death	Observed number of deaths	Expected proportion	Expected number of deaths	Observed/ expected ratio
Cardiovascular	63	.460		
Cancer	31	.160		
Pulmonary	10	.050		
Digestive tract	3	.050		
Liver/Biliary	* 4	.005		
Leukemia/Lymphoma	4	.020		
Brain	4	.010		
Other	6	.025		
Cirrhosis of liver	4	.025		
Accidents	7	.020		
All other causes	39	.335		
Total	144	1.00		

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* Note that specific cancer sites are subsets of the total 31 cancer deaths.

Question 4

a) Calculate the expected number of deaths and an observed/expected mortality ratio for each diagnostic category.

b) How would you interpret the results?

c) How might the results be misleading?

THE COHORT STUDY

The cohort study was conducted by abstracting all available medical and work-history information on each worker, past and present, ever to work at each of the four plants. The specific jobs performed by each worker, the dates of starting and ending each job, and the age at the start of employment were recorded. Each worker was then traced to determine cause of death.

Question 5

What means might have been used to achieve follow-up of each worker?

The next step in the cohort study involved construction of a table of person-years at risk for disease for members of the cohort. Observed and expected mortality was then compared for specific causes of death within the cohorts using these person-year totals as denominators. The basic principles by which the cohorts were assembled can be illustrated by reviewing the work histories of 10 different hypothetical workers.

Worker No. 1: Began work in 1944 at 20 years of age. Had worked up to the present in PVC polymerization.

Worker No. 2: Began work in 1944 at 20 years of age. Worked until August 1949 as a pipefitter and left that employment.

Worker No. 3: Began work in 1944 at the age of 35 years. Had worked up to the present in PVC polymerization.

Worker No. 4: Began work in 1944 at 20 years of age. Died in 1969. Worked in PVC polymerization.

Worker No. 5: Began work in 1944 at 20 years of age. Had worked to the present in administration, becoming vice president in charge of sales.

Worker No. 6: Began work in 1946 at the age of 52 years. Died in 1947. Worked in PVC polymerization.

Worker No. 7: Began work in 1972 at 21 years of age. Had worked to the present in PVC polymerization.

Worker No. 8: Began work in 1944 at 20 years of age. Worked for three weeks in PVC polymerization and then was drafted into the Army. Returned in 1954 at the age of 30 years and worked in PVC polymerization until October 1956 when he ceased that employment.

Worker No. 9: Began work in 1944 at the age of 40 years. Worked in PVC packing and shipping. Retired in 1969.

Worker No.10: Began work in 1965 at the age of 20 years. Had worked to the present in PVC polymerization.

Question 6

A modified life-table method is used to determine the total number of person years at risk of developing disease stratifying by age and decade of observation. The chart is listed below.

a) Complete the following chart to show person-years at-risk for developing disease for all these ten persons. The person-years contributed by Workers Nos. 1 and 2 have been entered for illustration purposes. (For sake of simplicity, consider partial years as whole years).

	Decade of observation			
Age in years	1944-1953 Workers No.	1954-1963 Workers No.	1964-1973 Workers No.	Total
20-29	1-10 2-10			
30-39		1-10 2-10		
40-49			1-10 2-10	
50-59				
60-69				
Total				

b) Why do person-years continue to accumulate after the worker leaves work or retires?
c) When would the person-years stop accumulating?
d) How is this information to be used?
e) What would be the effect of loss to follow-up?

PART 3

Obviously, different workers have different work histories and hence contribute unequally in terms both of exposure to VCM and of latency since their first VCM exposure. Some have worked directly in polymerization for many years (Workers Nos. 1, 3 & 4), others for shorter time periods (Workers Nos. 6, 7, 8 & 10). Some have had less direct contact with polymerization (Workers Nos. 2, 5 & 9), again for varying periods of time. To make the cohort study as meaningful as possible, it is necessary to give particular attention to the mortality experience of workers closely exposed to VCM over a substantial period of time, with an initial exposure long enough ago to allow for reasonable carcinogenesis latency. The review of the actual work histories of the initial four cases is a useful starting point for establishing criteria of job category, exposure duration, and latency. The following chart has been completed for the ten hypothetical workers. After examining this information, learning about the natural history of cancer, and investigating the work practices, the investigators decided on requirements for entry into the cohort. Entry into the cohort required five years of VCM exposure in a production areas of the plant, and ten years of latency.

Age in years	1944-1953 Workers No.	1954-1963 Workers No.	1964-1973 Workers No.	Years of exposure	Total
20-29					0
30-39		1-10 2-10 4-10		30	
40-49		3-5	1-10 2-10 4-6	31	
50-59		3-5 9-10	3-5	20	
60-69			3-5 9-10	15	
Total years of exposure	0	50	46	96	

Question 7

How would this chart of "high-risk" person-years compare with one in which all person-years are included regardless of exposure, latency, and job category?

Question 8

What workers were eliminated? Why?

Question 9

a) What is the effect of including Workers Nos. 6 and 7 in the "high-risk" chart?
b) What is the effect of including Worker No. 10 in the "high-risk" chart?
c) How is latency to be defined for Worker No. 8?

Assuming a criterion of five-years' exposure, the total person-years at risk for disease in the actual cohort are shown by age in Table II for persons with less than and more than ten years' latency. Follow-up was virtually complete (1287 out of 1294 members of the ten-year latency group). In these two groups, a total of 5 and 35 cases of cancer were observed. Included for comparison are 1965 age-specific mortality rates for cancers of all sites in US white males.

Table II. Total person-years at risk for disease

	Person-years at risk disease for workers with latency of		Expected age specific cancer mortality	Expected number of cancer deaths for latency of	
Age in Years	less than 10 years	more than 10 years	per 100 000	less than 10 years	more than 10 years
20-29	8444	38	13		
30-39	4619	3065	28		
40-49	2180	5668	91		
50-59	508	2681	300		
60-69	40	1078	712		
70-79	0	171	1223		
80+	0	20	1710		
			Total expected deaths		
			Total observed deaths	5	35
			SMR (O/E X 100)		

Question 10

a) For each latency group, calculate the expected numbers of deaths in each age category, and then an overall standardized mortality ratio (SMR).

b) How do you interpret these results in terms of cancer risk among persons exposed to VCM?

The actual computation of expected numbers of cases was far more complex than the above illustrations suggest. Person-years at risk for disease were counted using 5-year rather than 10-year groupings by age. Expected numbers of deaths were calculated using mortality rates for 5-year periods from 1940 to the present, rather than a single set of rates for a given median year (1965). The results of these calculations are shown in Table III.

Table III. Number of deaths among workers
with five or more years VCM exposure
and ten or more years latency

Cause of death	Observed	Expected	Standardized mortality rate
Cardiovascular	57	54.7	______
Cancer	35	23.5	______
Pulmonary	12	7.7	______
Liver/Biliary	7	0.6	______
Leukemia/Lymphoma	4	2.5	______
Brain	3	0.9	______
Other	9	11.8	______
Cirrhosis Of liver	2	4.0	______
Pulmonary disease (excluding cancer)	6	3.4	______
Violent deaths	13	14.2	______
All other causes	22	26.5	______
Unknown cause	1	---	--
Total	136	126.3	______

Question 11

a) Why is it preferable to use mortality rates from several different time periods rather than from one year in computing expected mortality?
b) Why are 5-year groupings by age preferable to 10-year groupings?

Question 12

a) Compute an SMR value for each cause-of-death category.
b) How would you interpret these results?
c) How might the results be affected if different criteria were used for exposure (1, 2 or 10 years instead of 5) or for latency (5 or 15 years instead of 10)?

Question 13

What further studies should be undertaken in light of these results?

Question 14

If a repetition of this study would yield a negative result in another country, what reasons for this could you think of?

INSTRUCTOR'S NOTES
VINYL CHLORIDE AND CANCER

OBJECTIVES

1. How to deal epidemiologically with a cluster of rare disease.
2. How to choose the appropriate study design.
3. How to choose the appropriate study population.
4. Introduction to the proportional mortality ratio.
5. Introduction to the cohort study including the concept of person years.
6. Understanding latency and exposure categorization.

PART 1

Answer 1

Calculate a rough value of crude mortality ratio of ASL for long-term PVC polymerization workers at this plant in the past 10 years, assuming 10 years at-risk for each worker and a US population of 200 million.

Crude mortality ratio = Cases/person-years (exposed) = 4/(500X10) = 0.0008
Cases/person-years (general population)=27/(200 000 000)
= 0.00000135
= x 5926 excess

Instructors note Make sure that the students are familiar with the definition of person-years at risk. "At risk" refers to years of observation when the person is eligible to develop the disease of interest.

Answer 2

What further questions are raised both by the finding of four cases of ASL at one plant and by the appearance of ASL and other tumours in rats exposed to VCM?

a. PVC industry - So far, cases were from just one plant. Are other plants involved? Is this an industrywide problem? Are there special risk-factors besides VCM exposure at the Louisville plant?

b. Diagnosis - Rare tumours are easily misdiagnosed. Would a careful review of records reveal more cases than are initially apparent? What is the true risk for exposed workers? Are there precursor stages of ASL which could be identified (e.g. liver damage)?

c. Outcomes - The animal studies suggest that a multiplicity of tumours result from VCM exposure. Is this true for exposed persons also?

d. Public health - PVC is widely used. What risk is there, if any, for 1) consumers, 2) persons living near VCM/PVC production or fabrication facilities or for persons employed in the many industries which manufacture PVC-containing products? It might be useful to ask one or more students to review the process in advance, and to comment on the major sources of exposure, and exposure levels in his or her country.

Answer 3

a) Given these facts, what phase of the VCM/PVC industry would be best suited for an epidemiological study of VCM health effects? Why?

Considerations

1. Exposure - studied populations should have had exposure to VCM.
2. Population size - sufficient size to provide some acceptable power to the study (add power calculation).
3. Records - available records and tracking of the population. The workforce in the polymerization phase would be the best to study, given the size of the workforce and their extent of exposure.
4. Latency.
5. Same plant/industry wide - cluster problem.

b) Why conduct further epidemiological studies of this population?

There are three answers to this: 1) to quantify the magnitude of the cancer excess in the population in which the cluster was originally observed; 2) to determine whether other malignant or nonmalignant diseases are also in excess, other than the original sentinel tumour; 3) if one wanted to confirm the association between vinyl chloride and ASL, independent of the original cluster, one would theoretically need to exclude the original cases or go to an entirely new study population. If the presenting tumour had been more common, this would be more necessary than with an extremely rare tumour such as ASL.

c) What kind of study might be undertaken? Why?

The discussion should address at least three issues involved in choosing the most appropriate study design. First, what are the advantages of basing the study upon exposure (cohort approach) or disease (case-referent approach)? Second, should the period of observation be prospective or retrospective? A prospective approach would allow the collection of high quality exposure data, but would be expensive and would not provide results for at least ten years. Third, should the measure of disease be cancer incidence (morbidity) or death (mortality)? For angiosarcoma, mortality approximates to morbidity because of the lethality of the disease.

To return to the issue of whether a cohort or case-referent study design is preferable, the latter is usually said to be more efficient if the disease is rare. However, a cohort study in this highly exposed group of workers could be used to quantify the excess, initially apparent, as a cluster. Alternatively, a case-referent study in a defined geographical area, e.g. a nation, could be conducted if there were a means of identifying cases. This approach might miss the contribution of a rare exposure if there are other, more common causes of the disease.

d) What criteria would you suggest for selecting groups of workers for the study?

Since cancers are likely to require a long latent period after the first chemical exposure, only those plants in operation for many years should be studied, and preferably those making pure PVC (and relatively few copolymers). Particular attention should be given to the workers involved, first, in reactor-cleaning and, second, in direct handling of fresh PVC. Attention should be given to the ultimate size of the cohort, to the feasibility of retrieving records at given plants, to the ease of tracking workers in particular areas, and to the existence of industrial hygiene that would characterize prior exposure.

If positive findings come from the study of polymerization workers, consideration might be given to a study of less exposed phases of the industry and of the consuming public.

PART 2

Answer 4

a) Calculate the expected number of deaths and an observed/expected mortality ratio for each diagnostic category.

Table IV. Proportional mortality ratio

Cause of death	Observed number of deaths	Expected proportion	Expected number of deaths	Observed/ expected mortality ratio
Cardiovascular	63	.460	66.24	0.95
Cancer	31	.160	23.04	1.35
Pulmonary	10	.050	7.20	1.39
Digestive tract	3	.050	7.20	0.42
Liver/Biliary	4	.005	0.72	5.56*
Leukemia/Lymphoma	4	.020	2.88	1.39
Brain	4	.010	1.44	2.78
Other	6	.025	3.60	1.67
Cirrhosis of liver	4	.025	3.60	1.11
Accidents	7	.020	2.88	2.43*
All other cases	39	.335	48.24	0.81
Total	144	1.000	144.00	1.00

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* Significant $p = 0.05$, using a "simple" Chi-square test, i.e. $\frac{(\text{observed number} - \text{expected number})^2}{\text{expected number}}$

68

A more accurate test would be the Mantel-Haenszel summary chi square used on age standardized data. This, however, requires age data which are not given in this problem.

b) How would you interpret the results?
   There is an excess of cancer (especially of the liver and brain) and also an excess for accidents.

c) How might the results be misleading?
   1. A proportional mortality analysis compares proportions and not rates. If mortality rates for causes other than cancer were relatively low among PVC workers, the proportion of cancer deaths might appear excessive without any real increase in rates.

   2. The 144 deaths may not be representative of all deaths within the cohort.

   3. Data came from medical and insurance records at each plant. No independent appraisal or review of cause of death was made.

   4. The comparability was somewhat controlled in being restricted to white males and adjusted for age and year of death. However, there is always some concern about comparing a healthy working population to general US population mortality data.

ANSWER 5

5. What means have been used to achieve follow-up of each worker?

   Records of company, union, pension, Veterans Administration, social security, state motor vehicle, credit bureau.

ANSWER 6

6. a) Complete the following chart to show person-years at-risk for these ten persons. The person-years contributed by workers No. 1 and 2 have been entered for illustration purposes.

Note: The purpose of this exercise is to practice calculating person-years at risk. Do not worry about excluding anyone by title, work history, or latency.

Age in years	1944-53 Workers Nos.	1954-63 Workers Nos.	1964-73 Workers Nos.	Total person-years
20-29	1-10		7-2	
	2-10		10-9	
	4-10			
	5-10			
	8-10			61
30-39	3-5	1-10		
		2-10		
		4-10		
		5-10		
		8-10		55
40-49	3-5	3-5	1-10	
	9-10		2-10	
			4-6	
			5-10	
			8-10	66
50-59	6-2	3-5	3-5	
		9-10		22
60-69			3-5	
			9-10	15
Total person-years	72	70	77	219

b) Why do person-years continue to accumulate after the worker quits or retires?

A worker is continually followed and is at risk of developing the disease even after quitting, retirement, or lack of further VCM exposure. Note that for study purposes, he is only followed after he has achieved sufficient exposure and latency as defined by the study (in this case five years exposure and ten years latency).

c) When would person years stop accumulating once adequate exposure time has been acquired?

1 - When the worker dies. Note that if the worker dies prior to a sufficient latency period, he is not included in the study.
2 - When the study ends; in this case 1973.

d) How is the life-table information to be used?

Person-years are accumulated as the denominator for rate calculations.

e) What would be the effect of loss to follow up? Consider fewer person-years for any statum selection, and different accuracy of diagnosis in different geographical areas.

PART 3

Answer 7

How would this cohort of "high-risk" person-years compare with one in which all person-years are included, regardless of exposure, latency, and job category?

It contains less than half the total person-years, none from the early decades and none for persons in their the age group 20-29. This cohort definition (five years' exposure, ten years' latency) is arbitrary, but reasonable. It can be changed as circumstances warrant it.

Answer 8

What workers were eliminated? Why?

No. 5 - administrative job; no VCM exposure.
No. 6 - insufficient exposure time; insufficient latency.
No. 7 - insufficient exposure time; insufficient latency.
No. 8 - insufficient exposure time.
No.10 - insufficient latency.

Answer 9

a) What would be the effect of including each worker in the high-risk chart? No. 6 - dilute the overall person-year total with two years without representing an appreciable risk of a work-related cancer, and his death would falsely exaggerate mortality in whatever his cause of death category was, again being unlikely to be job-related illness.

No. 7 - dilute the overall person-year total without representing appreciable risk of a work-related cancer.

No. 10 - again, dilute the person-year total without having sufficient latency to be eligible of a work-related cancer.

b) How is latency to be defined of Worker No. 8?

Worker No. 8 does not meet the five years' exposure criterion necessary to be included in the "high-risk" chart. Therefore, defining latency is meaningless in this case.

In general, latency is defined as the interval of time ending with death (or study end date, whichever come first) and beginning with the first exposure.

Answer 10

a) For each latency group, calculate expected numbers of deaths in each age category, and then an overall standardized mortality ratio (SMR).

Age in years	Expected number of cancer deaths for latency of less than 10 years	more than 10 years
20-29	1.098	0.005
30-39	1.293	0.858
40-49	1.984	5.158
50-59	1.524	8.043
60-69	0.285	7.675
70-79	0	2.091
80+	0	0.342
Total expected deaths	6.184	24.172
Total observed deaths	5	35
SMR (O/E X 100)	80.85	144.79

b) How do you interpret these results in terms of cancer rates among persons exposed to VCM?

These results indicate fewer cancer deaths than expected in the short latency group (reflecting the fact that one needs to be healthy to hold a job [Healthy worker effect]), but more than expected for long latency, perhaps indicating oncogenic effects of VCM or other work- place chemicals. Also, the excess of cancer is not merely a result of the four liver cancers alone. The SMR applies specifically to this cohort, and cannot be directly extrapolated to other cohorts (past or present), although it is a good indicator of risk in similarly exposed groups.

Answer 11

a) Why is it preferable to use mortality rates from several different time-periods rather than from one year in computing expected mortality?

For some causes of death (e.g., stomach or lung cancer), mortality rates have changed greatly over the past several decades.

b) Are 5-year groupings by age preferable to 10-year groupings?

Since the risk of death from particular causes may change markedly with age, especially at older ages, the use of individual year- groupings is preferable.

Answer 12

a) Compute the SMR value for each cause-of-death category.

Cause of death	Observed	Expected	SMR	95 % Confidence limits +
Cardiovascular	57	54.7	104	79-135
Cancer	35	23.5	149*	104-207
Pulmonary	12	7.7	156	80-272
Liver/Biliary	7	0.6	1167**	467-2404
Leukemia/Lymphoma	4	2.5	160	51-386
Brain	3	0.9	333	85-907
Other	9	11.8	76	35-145
Cirrhosis of liver	2	4.0	50	8-165
Pulmonary disease (excluding cancer)	6	3.4	176	64-384
Violent deaths	13	14.2	92	49-157
All other causes	22	26.5	85	52-126
Unknown cause	1			
Total	136	126.3	108	90-127

+ For the ratio of an observed value of a Poisson variable to its expectation.
* p = 0.05
** p = 0.01 Poisson chart 99% confidence intervals 41-343.

b) How do you interpret these results?

Cancer mortality is significantly increased. Numbers are small, however, and only liver tumours show statistically significantly excesses. Excesses present for lung, leukemia, and brain may deserve further study. The SMR for total cancer is remarkably similar to the simplified illustration (149 versus 145) and the overall results are basically similar to those obtained in the proportional mortality analysis. For validity and comparability arguments, see note 4c above.

c) How might the results be affected if different criteria were used for exposure (1, 2, or 10 years instead of 5) or for latency (5 or 15 years instead of 10)?

Longer exposure and latency criteria might have increased the SMR values, but at a loss of numerical/statistical strength. Shorter periods would increase numerical strength, but dilute the results.

Answer 13

What further studies should be undertaken in light of these results?

While mortality excesses may be too small to warrant similar cohort studies in less exposed workers or in general population groups, a detailed study of individual cancer cases in polymerization workers may be useful. Specific clinical, pathological, and work-history features of such cases (especially liver, and possibly brain and lung) may provide further clues to etiology. Additional animal-exposure experiments are also needed. Studies on other vinyl chloride related diseases are desirable.

Answer 14

If a repetition of this study yielded a negative result in another country, what reasons for this could you think of?

For example, lower exposure levels, too short exposure times, poor record-keeping system, population at risk too small.

Reference

Viola, P.L., Bigotti, A. Caputo, A. Oncogenic response of rat skin, lungs and bones to vinyl chloride. Cancer research, 31; 516-522 (1971).

OCCUPATIONAL NEUROLOGICAL DISEASE *

PART 1

On 2 October 1973, the Deputy Director, Ohio Department of Health contacted the Director, Cancer and Birth Defects Division, Bureau of Epidemiology, Center for Disease Control (CDC), Atlanta, USA, to request assistance in investigating an apparent epidemic of peripheral neuropathy in workers at a coated fabric plant in Columbus, Ohio. He reported that cases of neuropathy had first been recognized in plant workers in July 1973 and that some 25 cases had been reported by early October. Emergency discussions were held involving the Bureau of Epidemiology, the National Institute for Occupational Safety and Health (NIOSH), and the Division of Neurology, Ohio State University (OSU) Hospitals, and it was agreed that a combined CDC-NIOSH-OSU investigation should be conducted. Accordingly, an epidemiologist and an epidemiology-elective student were dispatched from Atlanta to Columbus on 3 October.

Question 1

Studies involving investigators from many institutions (Federal, State, University, WHO, etc.) are potentially chaotic. If you were the epidemiologist assigned to this project, what would you recommend to minimize confusion and to improve collaboration?

Question 2

Given what you have been told, what are the first steps your investigation must take?

PART 2

The following is a description of the plant:

Columbus Coated Fabrics (CCF) occupies a 6.5 hectare site on the edge of an industrial district in north-central Columbus. The plant employed between 850 - 950 hourly employees and about 200-300 salaried employees. Various types of vinyl coated fabrics comprised CCF's products. Principally, they produced plastic wall cloths with many elaborately printed and embossed designs. They also supplied car manufacturers with vinyl cloth used for making seat covers. Production began either with vinyl-coated cloth prepared by application of a freshly mixed vinyl solution to rolls of cloth, or with vinyl sheeting prepared by the extrusion of molten vinyl between rollers. These unfinished products were modified by printing, embossing, or by the addition of special surface coats.

---

* By Philip J. Landrigan, 1979; revised 1985.

The following is a description of the initial cases seen at Ohio State University Hospital:

In mid-August 1973, a 43-year-old employee of the CCF print department presented at the Neurology Service complaining of having been weak since May. Neurological examination and clinical tests, including electromyography (EMG) and nerve conduction velocity (NCV), indicated a diagnosis of relatively acute peripheral neuropathy.

The patient revealed that five other employees in the print department had developed similar illnesses. All who had become ill by mid-August had similar clinical features, typified in the following synopsis:

> A 23-year-old male first noted intermittent tingling sensations in his arms and legs in April 1973. These symptoms would last four to five minutes at a time. In April or May, his right knee became stiff causing difficulty in walking. In August, he first noticed progressive weakness and stiffness of his fingers which necessitated the use of both thumbs to flip the wheel of a cigarette lighter and which made it impossible for him to turn the switch of a lamp. He complained of sweating, but had no bowel, bladder, or sexual dysfunction. A 10-kg weight loss since January 1973 was attributed to dieting.
>
> He admitted drinking two to three beers and smoking a pack of 20 cigarettes per day. He had had rheumatic fever at the age of 16. There was no significant family history. He had been employed in the print department at CCF for the past two and a half years.
>
> Physical examination revealed a slender young man in no acute distress. His mental status and cranial nerves were normal. He walked with a bilateral foot slap. Decreased pin prick, temperature, and light touch sensations were noted in a patchy distribution distally in the extremities. There was marked atrophy of the interosseous muscles, and a flexion deformity of the hands. Weakness of fingers and wrists was greater in extensors than in flexors. The weakness extended proximally to the shoulder, where he showed weakness of biceps, but normal triceps, as well as normal abduction, internal, and external rotation functions. He had bilateral foot drop with atrophy of the calves and thighs. Deep tendon ankle reflexes were absent, with other deep tendon reflexes symmetrically depressed or normal. The plantar response was flexor.
>
> Laboratory tests, including complete blood count, glucose, urea nitrogen, uric acid, alkaline phosphatase, serum glutamic oxaloacetic transaminase, lactic dehydrogenase, plasma cholinesterase, blood lead, blood arsenic, spinal fluid, and immunoglobulin G were normal. The cerebrospinal fluid contained no cells and showed normal protein and glucose levels.
>
> The right peroneal nerve conduction velocity was 35 m/sec, with normal faster than 45 m/sec. EMG showed evidence of denervation, with positive waves on insertion, fibrillation, and moderate to severe decrease in motor units in multiple distal muscles. The clinical diagnosis was severe peripheral neuropathy.

Question 3

Discuss the various etiologies that can result in peripheral neuropathy.

Question 4

What is strikingly absent from this case history?

Question 5

With a diagnosis of acute peripheral neuropathy apparently well established in these initial cases, how would you proceed to further characterize the outbreak?

Question 6

Would it be appropriate to search for the possible occurrence of subclinical cases of neuropathy?

PART 3

Electrodiagnostic screening was used to find additional cases at the plant. EMG and NCV examination was offered in the first instance to (1) all print shop employees, and (2) all employees of other departments who complained of neurological symptoms. However, EMG findings characteristic of motor unit disease were soon discovered in employees of other departments. The scope of the programme was therefore expanded, and an attempt was made to perform EMG's on all plant employees.

Electrodiagnostic examinations were done on 1162 persons (approximately 94% of the workforce). Of these, 182 persons with EMG's suggestive of peripheral neuropathy were referred for complete neurological examination and additional testing. All such persons were questioned about potential nonoccupational etiologic factors.

Of the 182 persons examined, five were excluded because they exhibited chronic neuropathies of unknown etiology not consistent with findings in the initial cases. Thirty-two others were found to have nonoccupational risk factors for their neuropathic findings:

diabetes mellitus	18
carpel tunnel syndrome	6
genetic/metabolic disorders	3
compression	3
radiculopathy	1
metabolic disorders	1

Forty-eight of the remaining 145 persons had definite clinical evidence of acute peripheral neuropathy, another 20 had equivocal findings, and 77 were judged on complete examination to exhibit no evidence of neuropathy.

Question 7

Would you have set up the screening programme in the way in which it was set up here?

Question 8

Would you have referred only the "positives" on electrodiagnostic screening for further neurological examination? What are gains and losses of such an approach?

Question 9

What is the case definition being used by the investigators?

Question 10

In your further analysis, what would you have done with the data from the 37 persons found to have other, non-occupational, risk factors for neuropathy.

Question 11

What would you have done with data from the 20 persons graded as having equivocal findings?

PART 4

The following is a summary of the epidemiological data on the 48 persons with definite neuropathy. The information on plant department at the time of onset was obtained by questionnaire, supplemented by review of the personnel records.

Case No.	Plant department	Month of onset
1	PX Inspection	7/72
2	Print	12/72
3	Print	1/73
4	Print	2/73*
5	Print	2/73
6	Print	3/73*
7	Print	4/73
8	Print	4/73
9	Embossing	4/73
10	Print	5/73*
11	Print	5/73*
12	Print	5/73
13	Print	6/73*
14	Print	6/73
15	Plastic calendar	6/73
16	Print	6/73
17	Print	6/73
18	Print	6/73
19	Print	7/73
20	Base coat	7/73
21	Print	7/73
22	Print	7/73
23	Print	7/73
24	Print	7/73
25	Mixing	8/73
26	Plastic calendar	8/73
27	Print	8/73*
28	South mill	8/73
29	Print	8/73
30	Print	8/73
31	Shipping	8/73
32	Print	9/73
33	Base coat	9/73
34	Print	9/73
35	North mill	9/73
36	Print	9/73
37	Print	9/73
38	Print	9/73
39	Print	9/73
40	Print	Indefinite
41	Print	Indefinite
42	Print	Indefinite
43	Print	Indefinite
44	Base coat	Indefinite
45	Print	Indefinite
46	Print	Indefinite
47	South coat	Indefinite
48	Print	Indefinite

---

*One of the 6 index cases

The nine persons with indefinite dates of onset specified that onset had occurred in the first ten months of 1973. No significant differences were found in prevalence by age groups, sex, or race. As with any epidemic, the characteristics of time, place, and person of those affected may provide clues as to etiology.

Question 12

Construct an epidemic curve, graphing the number of cases versus the date of onset. What mechanisms of disease transmission would be consistent with this type of epidemic curve? (common source? person-to-person?) Do you believe the absence of cases after September 1973?

Question 13

Calculate the prevalence of disease by department, using the following denominator data:

Department	No. of cases	No. of persons examined	prevalence
Print		167	
Base coat		45	
Plastic calendar		55	
Mixing		71	
Embossing		65	
PX inspection		37	
South mill		32	
North mill		16	
Shipping		31	
South coat		65	
Other		416	
Office		107	
Total	48	1107	

Question 14

What do these department-specific prevalences tell you?

Question 15

What additional information do you need to determine the etiology of the outbreak?

PART 5

EXPOSURE DATA AND INFORMATION ABOUT THE PROCESS

As a first step in assessing exposures at the plant, a walk-through tour was conducted and a map was prepared to describe the location of equipment and the work-sites of employees. Work procedures were observed. Lists of chemicals were reviewed for possible neurotoxins, but no known neurotoxins were found.

It was learned that between August and December 1972, plant management had made a major change in the composition of solvents used in print department ink composition in Columbus. Methyl butyl ketone (MBK) had been substituted for methyl iso-butyl ketone (MIBK) in the solvent formula. The approximate composition of the new formula was MBK 10% and methyl ethyl ketone (MEK) 90%, whereas the old formula had contained MIBK 10% and MEK 90%. No other recent changes had been made in plant operations.

Atmospheric sampling for organic vapours was conducted by the Division of Occupational Health of the Ohio State Department of Health, and by NIOSH. Using charcoal sampling tubes, 31 air samples were taken in the principle workshop areas and around the printing machines. Ventilation surveys were conducted to determine air flow patterns. Gas chromatography and mass spectrophotometry were done on bulk samples to determine the composition of each chemical and solvent.

All air samples taken in September 1973, while the printing department was still in operation, showed MEK concentrations above established standards. Highest MEK concentrations were recorded adjacent to printing machines. The airborne MBK concentration exceeded standards in one sample, also adjacent to the printing machines.

The investigators also learned that CCF operated a similar fabric-coating plant in Newark, California. Raw materials, products, machinery, and production techniques in Newark were generally identical to those of the Columbus plant. However, the company evaluated new materials and techniques at the Columbus plant before transferring them to Newark. Unlike Columbus, the Newark plant had never used MBK as a solvent ingredient in its printing process; only MEK was used.

Using additional exposure information, and personnel records at the plant, the investigators reclassified the Columbus workforce according to exposure to a number of industrial agents or processes in use at the plant.

82

Disease prevalence by selected chemicals or processes.

Chemical agents	No. of Cases	No. of exposed workers evaluated	Disease prevalence (%)
MBK/MEK	36	167	____
Surface coats with Organosol and rarely MEK	6	158	____
Latex and vinyl surface coats	0	25	____
Surface coats with MEK	0	13	____
Hot or fluid plastic	3	194	____
Ink and plastic mix	1	71	____
Inspection and storage upstairs or separate rooms	2	116	____
Outside plant	0	155	____
Total (excluding MBK)	12	732	____

Question 16

Calculate disease prevalence for each of these exposure categories. Does this analysis contribute anything to the circumstantial evidence already available implicating MBK as the etiologic agent?

Question 17

How would you explain the occurrence of cases outside of the print department if MBK exposure was limited to the print department?

Question 18

How might a study of the Newark, California plant corroborate the Columbus findings?

PART 6

The Newark print department employed 20 persons in the same job categories as at the Columbus print department. The occupational exposures of these workers were closely similar except for the absence of MBK. EMG's and NCV's performed on all print department employees at Newark in late September 1973 found no persons who met the criteria of neuropathy. A similar examination performed on approximately 20 additional Newark workers found no neuropathy. Although small, this parallel study at Newark provided an external worker-comparison group that is comparable in nearly every occupational exposure except for the absence of MBK.

Evaluating dose-response

Although circumstantial evidence already implicates MBK as the etiological agent, such evidence would be strengthened by the demonstration of a positive dose-response relation. If a causal relationship exists, increased exposure should be associated with increased in incidence, increased severity of illness, and decreased latency interval.

To roughly evaluate the dose-response, print shop workers in the Columbus plant were divided into five categories. Disease prevalence was then examined using job categories as a surrogate, qualitative measure of exposure:

The highest exposure in the print shop was experienced by operators. These workers were in constant contact with solvent vapours and had more frequent physical contact with the liquid solvent than other print department workers. Helpers performed the same tasks as operators, but left the machine frequently to obtain additional materials and rolls of cloth, thus reducing their total time of exposure to solvents. Foremen and supervisors had infrequent contact with solvents; the same was true of service helpers who primarily carried equipment and material within the department and throughout the plant. A special subgroup of service helpers were the pan washers, responsible for cleaning the ink pans with solvents. Although these workers, like the operators, had constant exposure to solvents, they were the only persons in the print department allowed to wear gloves, aprons, or face masks. Thus, their actual exposure was difficult to assess.

Question 19

Calculate the following job-specific prevalences:

Job	Ill	Total	Prevalence
Operator	22	61	______
Helper	8	47	______
Service helper	0	13	______
Supervisor	0	21	______
Pan washer	2	7	______

Question 20

Are these results consistent with the notion of dose-response?

Question 21

How do you explain the prevalences in the pan washers?

PART 7

Concluding comments

Four lines of evidence suggest that exposure to MBK was responsible for this outbreak of peripheral neuropathy: (1) the close temporal relationship between the occurrence of cases and the introduction of MBK into the plant; (2) the abrupt termination of the epidemic which occurred upon removal of MBK from the plant in September 1973; (3) the concentration of cases among employees at the plant's print department where MBK was used almost exclusively; and (4) the positive dose-response relationship in the print shop between intensity of exposure and the prevalence of neuropathy. The absence of cases from the Newark plant provides further supporting evidence of the etiological role of MBK.

Theoretically, it seems possible that MBK might have acted as a vehicle or potentiating agent for some other unidentified toxin. This possibility is remote, however, since the epidemiological evidence associating illness with MBK usage is quite direct and since MBK is a relatively inert substance which does not react readily with other chemicals. That the solvent properties of MBK might have increased absorption of some other toxin is unlikely since other solvents with similar properties (MEK, MIBK, and acetone) are widely available in both Columbus and Newark. The subsequent demonstration of neuropathy in rats exposed to MBK provided experimental support to the epidemiological evidence that MBK was directly responsible. The possibility that MBK in combination with MEK has an interactive or synergistic effect in humans cannot be tested by this investigation.

The neuropathy seen in Columbus closely resembles clinical illness produced by n-hexane in Japanese and American workers. Both n-hexane and MBK are 6-carbon aliphatic chains, the sole difference being beta oxidation of the chain in MBK. Bacterial enzyme systems have been shown to convert MBK to n-hexane, and vice versa. Such observations suggest possible avenues for further toxicological research and clearly indicate a need for such solvents to be closely screened for adverse health effects prior to their introduction into the industrial workplace.

Suggested reading

Billmaier, D, et al. Peripheral neuropathy in a coated fabrics plant. Journal of occupational medicine, 16:665-671 (1974).

Allen, N, Mendell, J.R., Billmaier, D.J., Fontaine, R.E., O'Neill, J. Toxic polyneuropathy due to methyl n-butyl ketone: an industrial outbreak. Archives of neurology, 32:209-218 (1975). (The final two write-ups of the Columbus outbreak.)

Hexacarbon neuropathy. Editorial. Lancet, ii:942-943 (1979). (Editorial comment on this and related neuropathic episodes.)

Cannon, S.B., et al: Epidemic Kepone poisoning in chemical workers. American journal of epidemiology, 107:529-537 (1978). (Epidemiological description of a devastating outbreak of occupational neurological disease.)

Landrigan, P.J., Wilcox KR, Silva J, Jr, et al. Cohort study of Michigan residents exposed to polybrominated biphenyls: epidemiologic and immunologic findings. Annals of the New York Academy of Sciences, 320:284-294 (1979). (Epidemiological description of a statewide episode of chemical exposure in which the absence of a demonstrable dose-response relation argued against a causal link between the exposure and alleged illness.)

Spencer, P.S., Schaumberg, H.H. eds. Experimental and clinical neurotoxicology. Baltimore, Williams and Wilkins, 1980. (The best text on the toxicology of peripheral neuropathy.)

INSTRUCTOR'S NOTES
OCCUPATIONAL NEUROLOGICAL DISEASE

Summary

This case is intended to illustrate the use of traditional cross-sectional methods of outbreak investigation to assess a cluster of occupational neurological disease. The progresssion of the investigation includes the following steps:

1) Confirming the diagnosis for the index case(s).
2) Identifying other unrecognized cases.
3) Establishing a case definition.
4) Characterizing the cases by person, place, and time.
5) Plotting an epidemic curve.
6) Computing and comparing disease prevalence (attack rates) between subgroups having different exposures.

This case provides a bridge between the methods of infectious disease epidemiology and chronic disease epidemiology. Methods of acute outbreak investigation work (effectively identify the causal agent) in this case, because the outbreak was extreme, had a fairly short latency, and the affected workers had not left the workforce. Methods for more complex situations would need to be introduced in other cases.

PART 1

Answer 1

Since no one person or agency is clearly in charge, the areas of responsibility should be agreed upon early. Open communication is a central need. Some components of it are:

a) to decide in advance who is responsible for each of the major components of the investigation;

b) to agree on method (and spokesperson) for approaching both management and workers - N.B. if the shop is unionized, international union as well as local union officials must be involved;

c) to agree on who speaks to the press; and

d) to agree on rules regarding the publication of results.

Answer 2

As in any outbreak investigation, the first two questions to resolve are:

a) Are the cases real?

b) Is there really an epidemic?

To answer these, sufficient clinical information is needed on the initial cases to confirm disease. Given the large number of cases, and low background occurrence of peripheral neuropathy, one may strongly suspect that an epidemic exists. Other necessary information includes the number of workers at the plant, the dates of onset of disease, common features shared by cases, etc.

Note- A student may ask at this point whether any recent changes had occurred in the plant processes or materials. Clearly this question is along the right track, but premature - try to hold the student off.

PART 2

It is useful to discuss the various etiologies of neuropathy at this point, both to engage the clinicians in the group, and to point out that the etiology of the outbreak should not be assumed to be toxic.

Answer 3

The possible considerations include both occupational and nonoccupational causes of neuropathy: Among the causes are:

a) bacteriotoxic - diphtheria, tetanus, leprosy, tuberculosis;

b) immunological - including Guillain-Barr syndrome;

c) mechanical - trauma, pressure effects, radiculopathies, disc disease, carpal tunnel syndromes;

d) toxic - arsenic, lead, mercury, organophosphates (e.g. parathion, leptophos, triorthocresyl phosphate), thallium, carbon disulfide, trichloroethylene, isoniazid, methyl alcohol, tetrachloroethane, acrylamide, vitamin B_{12} excess;

e) metabolic and nutritional - vitamin B_1 deficiency, folate or vitamin B_{12} deficiency, diabetes mellitus, myxoedema, porphyria, gout, amyloidosis;

f) vascular;

g) neoplastic - (e.g., paraneoplastic syndromes may include either sensorimotor or pure sensory neuropathy); and

h) degenerative.

The commonest cause of peripheral neuropathy in the USA is chronic alcoholism.

Answer 4

Little occupational history is provided.

Answer 5

Characterization of the outbreak.

- Case-finding is the next step of traditional outbreak investigation. The cases of the disease need to be systematically identified so that they can be characterized by "time, place, and person".

- Already existing sources of data such as plant sick lists including data on recent medical leaves of absence, plant nurse's records, records of nearby hospitals, union records, and worker's compensation data may be used. New data should be generated by interviewing and examining workers, as was in fact done in this study.

Answer 6

Subclinical cases

It is potentially very useful to search for subclinical cases. Subclinical alterations occur on a continuum with clinical disease. These might be expected among workers with short or low intensity exposure. Such early effects have been documented from exposure to lead, mercury, solvents, and pesticides. An important point is that subclinical neuropathy does in fact reflect tissue injury and is not merely a physiological adaptation to the presence of toxin.

The detection of subclinical cases in this outbreak would be accomplished through electrodiagnostic testing.

PART 3

Answer 7

The initial EMG/NCV screening programme provides an example of how not to go about screening a population for disease. Even if the investigators were correct that most of the apparent disease (and therefore the causal agent) was in the print shop, this approach would not yield a comparison population that had been screened in a comparable way. Changing course, and deciding to screen the entire plant did provide an internal comparison population. However, it is very unusual to have so many workers agree to a painful and invasive test. Systematically sampling workers from the non-print departments would have been a more efficient design than examining everyone.

Two other problems with this approach are 1) potential examiner bias (introduced by testing workers from the print shop and all self-reported, symptomatic workers first, and then workers from other areas later) and 2) potential underestimation of the magnitude of the outbreak, due to limiting the investigation to current workers. On the positive side, the 94% participation rate is quite remarkable.

Answer 8

Follow-up procedures. The theoretical problem of referring for follow-up only those persons found "positive" on EMG screening is that persons inappropriately screened as "negatives", (i.e., false negatives) will be lost to follow-up. In practice that should not pose a major problem in this situation. In this situation we have numerous cases of clinically apparent disease, so that losing some subclinical cases will still leave a substantial number of cases. In addition, since the investigators have included an abnormal EMG and NCV result as part of the case definition, these individuals would be lost anyway.

For some audiences, this may be a useful opportunity to discuss concepts of screening. Screening tests are the preliminary tests which are used to divide the population into those with high versus low probabilities of having disease. A definite diagnosis is determined by follow-up examination. An underlying problem in this investigation is that there is no "gold standard" by which to classify workers as diseased or not diseased. If one were available it might be possible to compare the efficacy (sensitivity and specificity) of a number of different screening tests.

The concepts of sensitivity and specificity are best visualized in terms of a 2 x 2 diagram:

		definitive examination	
		positive	negative
screening examination	present	a	b
	absent	c	d

The sensitivity of the screen is defined as $\frac{a}{a + c}$

The specificity of the screen is defined as $\frac{d}{b + d}$

False positives = b
False negatives = c

Answer 9

The case definition is not explicitly stated. Operationally, it involved some combination of electrodiagnostic, physical, and history findings.

Answer 10

What one does with the 37 persons with extra-occupational risk factors depends largely upon circumstances. In this investigation, they were excluded from additional analysis in order to ensure that the "cases" could only be explained by occupation. Had there been fewer cases, the investigators would have been unable to exclude these 37. In addition, by excluding them, they could no longer examine the interaction between occupational and other risk factors. A possible compromise would be to conduct the analysis with these 37 cases in and out of the analysis, and to see whether they make a difference.

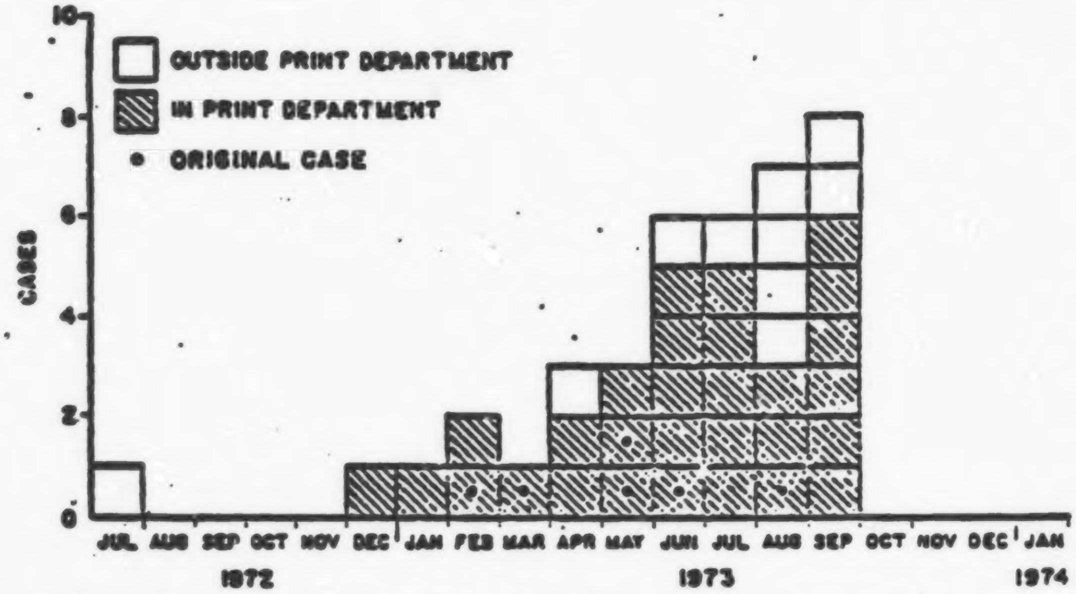
Answer 11

There is no best answer for this question. Because the disease status has been defined simply as either ill and well, there are invariably some individuals who are borderline. Excluding these might be too costly if one had few "cases". Under those circumstances, one could either relax the case definition or switch to a more efficient form of analysis, keeping the outcome data (EMG and NCV) as continuous. Under the present circumstances this group could be analysed separately to look for parallelisms between their epidemiological features and those of the 48 wit "definite neuropathy.

PART 4

Fig. 1 PERIPHERAL NEUROPATHY CASES,* BY MONTH OF ONSET

Answer 12



*9 CASES-DATE OF ONSET NOT AVAILABLE

Fig. 1. Peripheral neuropathy cases, by month of onset (nine cases - date of onset not available).

The temporal clustering of cases beginning in July 1972 is extremely informative, but the shape of the curve is not. The slow upslope of the epidemic curve could be consistent with either the gradual introduction of a common-source agent, the presence of a common-source with widely varying latency, or the occurrence of person-to-person transmission. This epidemic curve is chiefly useful in suggesting that cases were clustered in time, suggesting the introduction of a new agent or a change in the process. It would be helpful to confirm that there were no cases prior to July 1972, if plant medical or insurance records allowed you to do so. There is no indication whether the absence of cases after September 1973 is real, or a detection artifact due to the termination of the investigation.

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Answer 13

Table of prevalence by department

Department	No. of Cases	No. of persons examined	Prevalence (%)
Print	36	167	21.6
Base coat	3	45	6.7
Plastic calendar	2	55	3.6
Mixing	1	71	1.4
Embossing	1	65	1.5
PX inspection	1	37	2.7
South mill	1	32	3.1
North mill	1	16	6.3
Shipping	1	31	3.2
South coat	1	65	1.5
Other	0	416	0
Office	0	107	0
Total	48	1107	4.3
All departments excluding print	12	938	1.3

Answer 14

The prevalence of neuropathy in the print department was 21.5%, which is 16.5-fold higher than the prevalence in all other departments combined (1.3%). The difference in these proportions is statistically highly significant (p less than 0.001). These data suggest that the heaviest exposures to the offending substance occurred in the print department. (This question provides an opportunity to discuss the value of comparing disease frequencies as well as computing p values.)

Answer 15

Industrial hygiene data are the major missing pieces of information. Those data include information on exposures in the plant, and most importantly, information on recent changes in plant processes.

PART 5

Disease prevalence by selected chemicals or processes.

Chemical agents	No. of Cases	No. of exposed workers evaluated	Disease prevalence (%)
MBK/MEK	36	167	21.6
Surface coats with Organosol and rarely MEK	6	158	3.8
Latex and vinyl surface coats	0	25	0
Surface coats with MEK	0	13	0
Hot or fluid plastic	3	194	1.5
Ink and plastic mix	1	71	1.4
Inspection & storage upstairs or separate rooms	2	116	1.7
Outside plant	0	155	0
Total (excluding MBK)	12	732	1.6

Answer 16

The possible role of other chemicals was considered by examining the prevalence of neuropathy in persons exposed to various chemicals or processes. (Note - except for MBK, these categories overlap.) The prevalence of disease in the MBK area (print shop) was 21.6%, 13.5-fold higher than that in areas that were officially non-MBK (1.6%). This analysis contributes relatively little to the previous analysis of disease prevalence by department, except to show that workers exposed to other agents of potential concern (e.g., MEK alone) have much less disease than do those exposed to the MBK/MEK combination. (Note- it is impossible to separate MBK from the MBK/MEK combination, since MBK always occurs with MEK in this plant.)

Answer 17

Besides being present in print department ink, the MBK/MEK mixture was available at pump stations and in the mixing area in the print department for thinning ink and for clean-up operations. Employees of other departments occasionally "borrowed" the MBK/MEK mixture from the pump stations for minor clean-up operations; a case-by-case John Snow evaluation of exposures in cases from other departments might have been very informative. Otherwise, MBK had no uses in other departments in the Columbus factory.

Answer 18

Studies of the Newark, California plant.

The Newark plant provides an external comparison group that is totally free of MBK, but otherwise closely similar in other occupational exposures. (See additional information at beginning of Part 6.)

PART 6

Answer 19

Job-specific prevalences:

Department prevalence rates by job category.

Job	Ill	Total	Prevalence (%)
Operator	22	61	36.1
Helper	8	47	17.0
Service helper	0	13	0
Supervisor	0	21	0
Pan washer	2	7	28.6

Answer 20

Yes - these data are consistent with a dose-response relationship.

Answer 21

The two cases among the seven pan washers suggest that the protective equipment may have been ineffective.

LUNG CANCER IN CHEMICAL WORKERS*

PART 1

Bob Pontious, 44 year old chemical worker, father of five, nonsmoker, was referred to a chest physician in 1971. His symptoms were cough and haemoptysis. An oat cell or small cell bronchogenic carcinoma of the lung was found at surgery. Pontious informed the physician that, including himself, 14 of approximately 125 co-workers had lung cancer. The cases had occurred over many years in two units of a chemical factory where they mixed formalin, methanol, and hydrochloric acid in two, 3800 litre kettles to produce chloromethyl methyl ether (CMME). During the process fumes were often visible. To check for losses, the workers raised the lids on the kettles several times during each shift. The employees considered it a good day if the entire building had to be evacuated only three or four times per eight-hour shift because of noxious fumes.

Question 1

a) What occupational agents are known to cause lung cancer?
b) Suppose that you were the physician, that the date was 1971, and that you suspect that the lung cancers at this plant may be occupationally induced. How might you proceed?

PART 2

From the index case, other physicians, and the hospital charts of the other patients, the chest physician pieced together the following information (Table V).

Table V. Clinical information on the 14 reported cases of lung cancer

Case No.	Age at diagnosis (years)	Smoking history	Year diagnosed	Histological type
1	37	None	1962	Unknown
2	33	20 p.y.*	1962	Oat cell
3	39	20 p.y.	1962	Oat cell
4	47	20 p.y.	1963	Oat cell
5	52	10 p.y.	1964	Oat cell
6	47	21 p.y.	1964	Oat cell
7	43	20 p.y.	1966	Oat cell
8	53	40 p.y.	1969	Oat cell
9	48	33 p.y.	1970	Oat cell
10	50	30 p.y.	1970	Squamous
11	55	40 p.y.	1970	Oat cell
12	43	pipe	1970	Oat cell
13	37	None	1971	Oat cell
14	44	None	1971	Oat cell

*p.y. = pack-years

- Source - Figueroa, *et al*. 1973, Table I, p 1096.

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* By William Halperin, 1979; revised 1983.

Question 2

How is this additional clinical information useful?

PART 3

In the early 1970s, the histological distribution of lung cancer had not been well characterized, though Galofre and coworkers had made a classification in 1964 (Table VI):

Table VI. Approximate distribution of pathologic cell types of lung cancer in the general population*.

Pathologic type	Percentage of total
Bronchogenic cancer	90%
Squamous	63%
Adenocarcinoma	9%
Undifferentiated	18%
Large cell	(9%)
Oat (small) cell	(9%)
Bronchial adenoma	5%
Alveolar cell	2%
Mesenchymal	1.4%
Miscellaneous	1.5%

* Source - Galofre, M. el al. 1964.

Question 3

Assuming that this distribution reflects reality in 1971, how could the likelihood be quantified, that chance alone explained the observed fraction of oat cell cancers in the series? (For the purpose of this exercise, assume also that these 14 cases represent all of the cases of lung cancer that have occurred, and that cell type is not affected by age or other covariates about which we have no information.)

Question 4

In retrospect, in what year did this series become improbable?

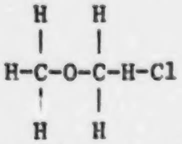
PART 4

Historical background

In actual fact, the management of the chemical plant in which these cases occurred did recognize an unusual cluster of lung cancer cases in 1962. They submitted a list of 102 chemicals used at the plant to a toxicologist to determine if any were known carcinogens. This review was unhelpful, since the causative agent was not known to be carcinogenic at the time. They also initiated a screening programme of semiannual chest x-rays for workers in the area of the plant where the first three cases had appeared.

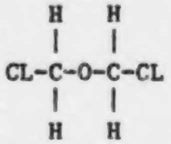
In 1964, as cases continued to occur, a team of toxicologists toured the industrial site. They suspected either CMME or bis-chloromethyl ether (BCME) as the causative agent. BCME is a contaminant in the manufacture of CMME accounting for 1-7% of total volume. The formulas of CMME and BCME are:

CMME



$$H-\overset{H}{\underset{H}{C}}-O-\overset{H}{\underset{H}{C}}-H-Cl$$

BCME



$$CL-\overset{H}{\underset{H}{C}}-O-\overset{H}{\underset{H}{C}}-CL$$

In 1965, the US National Cancer Institute (NCI) funded carcinogenicity studies of these agents. The results were reported by Van Duuren, et al. in 1968. These studies showed that CMME was inactive as a carcinogen, but 13 of 20(65%) of mice exposed to BCME developed papillomas, and 12 of these 13 (92%) progressed to squamous cell carcinomas within 325 days. The report concluded that "The results to date indicated very clearly that BCME is a potent alkylating carcinogen for mouse skin, whereas CMME is inactive. However, continued testing of the latter compound may indicate weak carcinogenic activity."

Following the NCI study, the company sponsored further toxicological work including an inhalation study of mice, reported by Leong, el al. in 1971. Groups of mice were exposed to CMME (2 ppm), BCME (1 ppm), the known mouse carcinogen urethane (138 ppm), and plain air for six hours/day, five days/week, from 21 to 28 weeks. Lung tumours developed in 50% of the CMME exposed group, 55% of the BCME group, 94% of the urethane group, and 41% of the plain air group. The BCME group had a mean of 2.89 tumours per animal as compared to 0.87 for the air exposed, 1.53 for the CMME, and 54.2 for the urethane. The report concluded, "BCME must be considered an active carcinogen...the carcinogenic effect of CMME cannot be established due to the contamination of a small amount of BCME."

Also in 1971, the preliminary report by Laskin and coworkers of a follow-up to the NCI sponsored work was published. This was an inhalation study of 30 rats exposed to BCME (0.1 ppm) for six hours/day, five days/week, for 101 exposures. Five of the nineteen rats coming to autopsy had squamous cell carcinomas of the lung, five had aesthesioneuroepitheliomas arising from the olfactory epithelium. One had both.

Question 5

Given these findings, what public health actions are called for?

PART 5

In July 1971, representatives of industry, government, and academia met to discuss the toxicological findings, and to determine the future research and regulatory actions needed for BCME (Lemen, et al. 1976). NIOSH decided to conduct an industrial hygiene survey, and then a retrospective study of cancer incidence at a chemical plant in California which produced anion exchange resins. This process involved exposure to BCME as a contaminant. The purpose of the study was to determine whether a similar excess of lung cancer was occurring in plants other than the one in which the initial cluster had been noted. The number of exposed workers in this plant was small. Only 136 white males had achieved five years of employment in the plant between 1 January 1955, and 31 March 1972.

Question 6

Do you think that the California plant is old enough, and large enough to adequately determine the human carcinogenicity of BCME?

PART 6

Consideration of statistical power, or the probability of not overlooking an excess risk, is an important part of study design, since it influences whether a proposed study is likely to be large enough to answer the question of interest. The power of a study is the probability that a statistically significant association will be found, if the true value of the 'effect' (here the ratio of incidence rates) in nature is as it is hypothesized. It reflects the probability of not missing a real effect. Power can be described in a variety of statistical terms (such as 1 - Beta, or the probability of not making a Type II error), but these terms usually only confuse the nonstatistician. The purpose of this exercise is to communicate an intuitive understanding of power, by examining how power is influenced by a number of other study conditions.

Question 7

In follow-up (cohort) studies, such as that being proposed in California, statistical power is dependent upon four factors. What are these?

Estimating the power of the study

Let us assume for the sake of simplification that, in the present example, the incidence rate of lung cancer among the unexposed is 70/100 000 person-years, and that the workers at this California plant have accrued 700 person-years at risk. From this we can calculate that 0.49 incident cases of lung cancer would be expected just from the background rates of lung cancer.

Figure 2 shows the relationship between statistical power, the number of expected deaths, and the assumed level of 'effect'. In this instance, the level of effect is referred to as the 'relative risk', meaning more precisely the ratio of the incidence rate in the exposed to that in the unexposed. Although Figure 2 refers to the number of expected deaths, it works equally well for the number of expected incident cases.

Question 8

a) How do you interpret Figure 2?

b) Given an expected incidence rate of 0.49, what will be the approximate power of the study for an assumed rate ratio of 2, 5, and 10? (In our case, 0.49 represents the number of expected incident cases, not deaths, but the figure works just the same.)

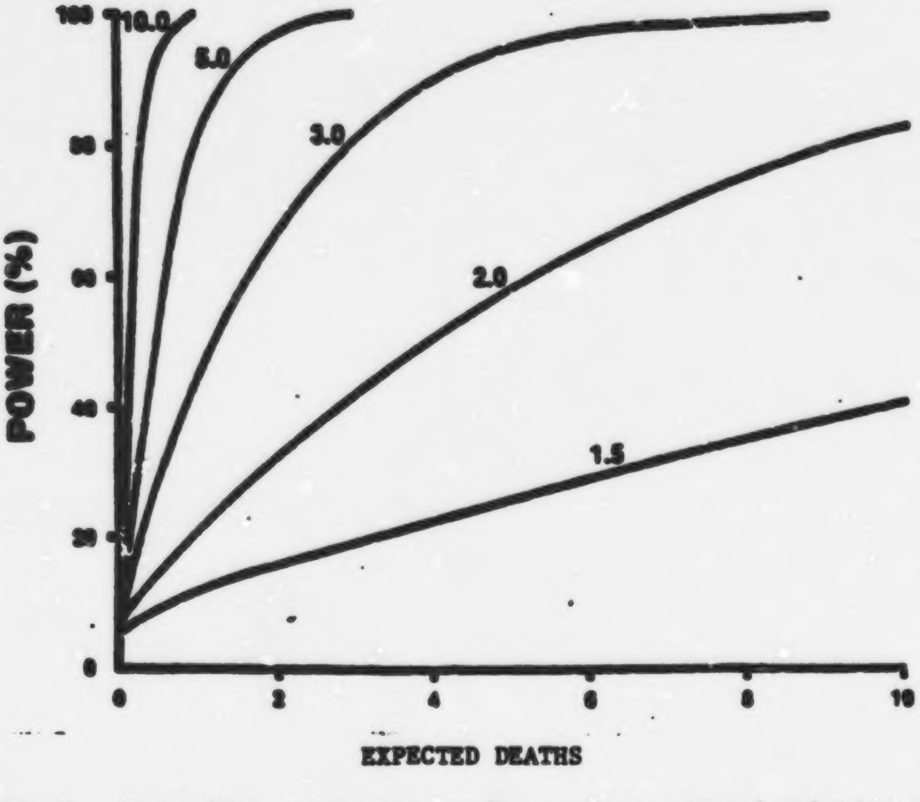


Figure 2. Approximate power curves for various assumed relative risks in standardized mortality ratio studies (for one-sided comparisons with alpha = 0.05). (From Beaumont & Breslow, 1981, p. 727).

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Interpretation. More important than being able to compute power is to understand the relation between power and the factors that influence it. Thus, statistical power increases as the size of the study population increases, as the hypothesized underlying rate ratio increases, or as the disease rate in the unexposed population becomes more common. Statistical power decreases with small study size, when the hypothesized underlying rate ratio is small, or when the disease is rare.

Considerations in study design. Usually, in choosing the sample size of a proposed study, the study population is considered large enough if it will allow detection of a reasonably small effect (e.g. a rate ratio of two or more) with a power of above 80%. Clearly the statistical power of the present study will be substantially below that. Although it is possible that the underlying rate ratio is large enough so that the study will be positive despite the small sample size, there is at present no data to support this possibility.

Question 9

What are the options open to the NIOSH investigators proposing to study the California plant?

It should be noted that NIOSH did conduct a retrospect cohort study of cancer incidence at the California plant. Their results were made public in May 1973. The NIOSH study reported a ninefold increase in the incidence of all respiratory cancer among 136 white males employed for at least five years between January 1955 to March 1972. Mean latency among the cases was 14.6 years, suggesting that the epidemic had probably not ended. The study by the chest physician included results of the prospective surveillance of cancer incidence, conducted by the company from 1963-1968. This showed an eight-fold increase in lung cancer when incidence rates were compared to those of the Philadelphia Pulmonary Neoplasm Research Project (Figueroa, et al. 1973). Also in May 1973, the Occupational Safety and Health Administration promulgated the Emergency Temporary Standard for 14 carcinogens, including BCME. A closed system was mandated with no detectable exposure allowed.

A further study, supported by the NIOSH, was an industrywide one covering nearly 2000 chloromethyl ether-exposed workers which confirmed the clear dose-response relationship of the compound and cancer amongst employees of some of the manufacturers involved (Pasternak, et al. 1977).

INSTRUCTOR'S NOTES

LUNG CANCER IN CHEMICAL WORKERS

This case-study illustrates several important epidemiological and public health concepts in the context of a remarkable and tragic outbreak of occupational cancer. These include:

1) The potential value of examining cell type in studying occupational carcinogens.

2) An application of the binomial distribution in quantifying the improbability of clusters of an unusual cell type, when the usual distribution is known.

3) The importance of making the results of occupational epidemiological investigations available to the general public and scientific community as soon as possible, so that critical review and timely intervention can be begun on an industrywide scale.

4) The importance of instituting control measures even while scientific uncertainty remains.

5) The importance of consideration of statistical power in planning whether a proposed study is large enough to answer the questions it is intended to address.

Answer 1

a) Some examples are arsenic, asbestos, acrylonitrile, bis-chloromethyl ether (BCME), chromium, coke oven emissions, haematite, nickel, nitrogen mustard and other alkylating agents, radon daughter emissions (from decay of uranium), and vinyl chloride (For a more complete list and documentation, see Table VII).

b) The practical options available in 1971 were somewhat different than those available today. Despite the passage of the Occupational Safety and Health Act in 1970, neither Occupational Safety and Health Administration nor NIOSH existed in their present form. There was no access to plant records to determine the denominator (person years at risk), nor would a physician's clinical training suggest the need for a retrospective cohort mortality study. Another practical option was for the company to embark on epidemiologic, industrial hygiene, and toxicological studies in collaboration with university based consultants, which is what they did.

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TABLE VII. INDUSTRIAL AGENTS ASSOCIATED WITH CANCER

A. Federally regulated carcinogens

	ANIMAL STUDIES			CLINICAL AND EPIDEMIOLOGIC STUDIES				
Agent	Species	Route of absorption	Target organs and tissues	Route of absorption	Latency (years)	Relative risk	Target organs and tissues	Comments
Asbestos fibres	Rat Rat Rat, hamster, rabbit	p.o. Inhalation Intrapleural	Multiple Lung, mesothelioma Mesothelioma	Lung Oral	15-50	1.5-12 100+ 1.5-3	Lung Mesothelioma Gastrointestinal tract (esophagus, stomach and large intestine)	Lung cancer synergism between asbestos and cigarette smoking. Because of rarity of mesothelioma in absence of asbestos exposure relative risk estimate has limited meaning. The number of potentially exposed workers is some 1.6 million. Current estimates of proportionate mortality in heavily exposed workers are lung cancer (20-25%), mesothelioma (7-10%) and gastrointestinal cancers (8-9%).
Occupation: Asbestos miners; asbestos textile makers; vehicle brake repairers; cement mixers; construction workers; cutters and layers of water pipes; insulation cord makers; insulators; shipyard workers								
Coke oven emissions (aromatic hydrocarbons including benzo (a)-pyrene)	Multiple	Skin Intratracheal	Lung Local sarcomas, lung			2.7	Lung Kidney	Animal studies refer to benzo(a) pyrene though other aromatic hydrocarbons found in emissions are also carcinogenic in various animal systems. Risk of lung cancer in humans increases with duration and intensity of exposure.
Occupation: Coke oven workers								
3,3'-dichlorobenzidine and its salts	Rat Hamster	p.o. p.o.	Multiple sites including bladder	Lung Skin				No human cases in studies with exposure to pure compound, although cases have occurred with simultaneous exposure to benzidine.
Occupation: Pigment makers; polyurethane workers.								
4-dimethylaminoazobenzene	Rat Mouse	p.o. p.o.	Liver Liver	Lung Skin				No documented cases in man.
Occupation: Research workers*								
4,4'-methylene-bis-(2-chloroaniline (MOCA)	Rat Dog	p.o. p.o.	Liver, lung Negative	Lung Skin				No documented cases in man.
Occupation: Elastomer makers; epoxy resin workers; polyurethane foam workers								
α-naphthylamine	Dog Mouse Hamster	p.o. p.o., s.c. p.o.	Negative Inconclusive Negative	Lung Skin	22	8.4	Bladder	Some questions remain as to whether or not observed human carcinogenicity is due to contamination with -naphtylamine.
Occupation: Chemical synthesizers; dye makers; rubber workers								
-naphtylamine	Dog Monkey	s.c., p.o. p.o.	Bladder Bladder	Lung Skin	16	87	Bladder	Previously widely used in dyestuffs, as an anti-oxidant for rubber and in rubber-coated cables. Little commercial produc-

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102

	ANIMAL STUDIES			CLINICAL AND EPIDEMIOLOGIC STUDIES				
Agent	Species	Route of absorption	Target organs and tissues	Route of absorption	Latency (years)	Relative risk	Target organs and tissues	Comments
Occupation: Research workers*								tion since 1972.
2-acetylaminofluorene	Rat Dog Guinea pig	p.o. p.o. Negative	Liver Bladder, liver	Lung Skin				Early appreciation of carcinogenic potential averted commercial production.
Occupation: Research workers*								
4-aminodiphenyl	Mouse Dog	p.o. p.o.	Bladder, liver Bladder	Lung Skin	15-35		Bladder	Formerly used as a rubber antioxidant and as a dye intermediate No longer commercially produced. Fifty-three bladder tumours in 315 exposed workers; 1 case occurred with only 133 days of exposure
Occupation: Diphenylamine workers; research workers*								
4-nitrobiphenyl	Dog	p.o.	Bladder					No documented cases in humans. Exposure to 4-aminodiphenyl always occurs concurrently.
Occupation: Research workers*								
Benzidine and its salts	Mouse Dog	s.c.	Liver, ear duct intestine Bladder	Lung Skin Oral	16	14	Bladder	Medical personnel using benzidine to test for occult blood.
Occupation: Biochemists, dye workers; medical laboratory workers; organic chemical synthesizers, plastic workers; rubber workers; wood chemists								
-propriolactone	Rodents	Skin painting p.o.	Skin papilloma and sarcoma, stomach liver	Lung Skin				No skin cancer cases documented in man.
Occupation: Acrylate plastic makers; chemists; disinfectant workers; plastic makers; resin makers; viricidal agent makers								

* Early recognition of carcinogenic potential averted extensive commercial production. Most current exposures are in limited investigational settings.

	ANIMAL STUDIES			CLINICAL AND EPIDEMIOLOGIC STUDIES				
Agent	Species	Route of absorption	Target organs and tissues	Route of absorption	Latency (years)	Relative risk	Target organs and tissues	Comments
0 Vinyl chloride	Rat	Inhalation	Skin, lung, osteochondroma	Lung ?Skin	12-29	Marked 1.6(?)	Angiosarcoma of the liver Lung Brain	Full potential risk of cancer and of hepatobiliary tract disease in man is not yet established.
Occupation: Organic chemical synthesizers; polyvinyl resin makers, rubber workers								
Chloromethyl methyl ether (CMME)	Mouse	Skin, s.c	Carcinoma, sarcoma	Lung Skin	10-15	8	Lung	Small cell carcinoma. Human exposurus generally involve both CMME and BCME.
Occupation: Organic chemical synthesizers								
Bis(chloromethyl) ether (BCME)	Mouse	Skin, s.c	Olfactory esthesioneuroepithelioma, lung adenoma, papilloma, carcinoma		10-15	100	Lung	Small cell carcinoma.
	Rat	s.c.	Fibrosarcoma					
Occupation: Ion exchange resin makers, laboratory workers; organic chemical synthesizers, polymer makers								
Ethyleneimine	Rat Mouse	s.c. p.o	Sarcoma, kidney Liver, lung	Lung Skin				No documented human cases.
Occupation: Effluent treaters, organic chemical synthesizers, paper makers; polyethyleneimine makers, textile workers								
N-nitrosodimethy-	Rat	p.o , inhalation	Liver, kidney lung	Lung Skin				Carcinogenic in seven animal species. No information on chronic effects in man.
Occupation: Dimethylhydrazine makers; nematocide makers, solvent workers								

TABLE VIII. .INDUSTRIAL AGENTS ASSOCIATED WITH CANCER

B. Agents for which epidemiology or animal studies suggest carcinogenic potential

Agent	ANIMAL STUDIES			CLINICAL AND EPIDEMIOLOGIC STUDIES				Comments
	Species	Route of absorption	Target organs and tissues	Route of absorption	Latency (years)	Relative risk	Target organs and tissues	
Benzene	Mouse Unsuccessful attempts to produce leukemia experimentally.	s.c , skin	Negative	Lung Skin	6-14	2.5	Aplastic anaemia, leukopenia and thrombocytopenia Acute leukaemia Erythroleukaemia	Chromosomal aberrations may follow toxic exposures. Etiologic role in chronic leukemias is controversial, although causal relationship with aplastic anemia well established, and with acute leukemias highly suspect.
Occupation: Adhesive makers; asbestos product-impregnators; benzene hexachloride workers, burnishers, carbolic acid makers, chemists; chlorinated benzene workers, detergent makers; dry-battery workers, dye makers; furniture finishers; glue makers; linoleum makers; maleic acid makers; nitrobenzene makers; petrochemical workers, putty makers; rubber makers; styrene makers, welders; artificial leather makers and shoe workers								
Soots, tars, oils (mixtures of aromatic hydrocarbons including benzo(a) pyrene)				Skin Lung	9-23	2-5 1.3 2.3	Skin, scrotum Lung Bladder	Precise risk varies with nature of mixture and nature and route of exposure. Creosote, a complex mixture of phenolic and aromatic compounds, may act as a tumour promoter.
Occupation: Cable layers, coal, gas, coke and petroleum industry workers; coal tar and pitch workers; electrical equipment workers; fabric proofers, net fixers, optical lens grinders; waterproofers; wharfmen; wood preservers								
Isopropyl oil	Mouse	s.c., Inhalation	Lung		10	20	Respiratory tract Ethmoid sinus	
Occupation: Isopropyl alcohol makers								
Organochloride pesticides								Aldrin is metabolized to dieldrin Use of aldrin and dieldrin have been discontinued in the USA and many other countries. Human studies of aldrin, aramite, DDT and dieldrin are too limited to be conclusive. No epidemiological studies are available for heptachlor or mirex.
Aldrin	Rat Mouse	p.o.	Negative or inconclusive					
Aramite	Rat Dog	p.o. p.o.	Liver Biliary tract					
DDT	Mouse Rat,guinea pig Dog,monkey	p.o. p.o.	Liver Negative					
Dieldrin	Mouse Rat Dog,monkey	p.o p.o. p.o.	Liver Negative Inconclusive					
Heptachlor	Rat	p.o.	Inconclusive					
Mirex	Mouse	p.o.	Liver					
Occupation: Agricultural workers; insecticide manufacturers								

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B. Agents for which epidemiology or animal studies suggest carcinogenic potential

	ANIMAL STUDIES			CLINICAL AND EPIDEMIOLOGIC STUDIES				
Agent	Species	Route of absorption	Target organs and tissues	Route of absorption	Latency (years)	Relative risk	Target organs and tissues	Comments
Polychlorinated biphenyls	Mouse Rat	p.o. p.o.	Liver Liver	Skin				Twelve thousand persons estimated to have occupational exposures. Wider environmental exposures. Deleterious effects on mammalian reproduction. Human studies are too limited to permit conclusions as to carcinogenic potential. Ingestion in man has produced a syndrome consisting of chloracne, brown pigmentation of skin and nails, transient visual disturbances, swelling of eyelids with eye discharge, and gastrointestinal symptoms with liver abnormalities and jaundice.
Occupation: Cable coaters, capacitor producers, dye makers; electrical equipment makers; herbicide makers; investment casting processors; lacquer makers, paper treaters; plasticizer makers; resin makers; rubber workers; textile flame proofers; transformer workers, wood preservers								
Aniline	Multiple	p.o.	Negative	Lung Skin				No adequate data to indicate carcinogenicity of aniline in animals or man. Probably only aniline derivatives and not the parent compound are bladder carcinogens in man.
Occupation: Acetanilide workers; bromide workers, coal tar workers; disinfectant makers; dye workers; ink workers; leather workers; lithographers, nitraniline workers, perfume makers, photographic chemical makers; plastic workers; printers, rocket fuel makers; rubber workers, tetryl makers, varnish workers								
Auramine	Rat Mouse	p.o. p.o.	Liver Liver	Lung Skin	19.3	4.6	Bladder	
Occupation: Dye makers								
				Magenta		Rat	s.c.	Local sarcoma
Lung		23	Bladder	Rehn's (1985) original descrip-				tion of "aniline tumours" involved magenta manufacture. Other chemical intermediates may be implicated in the etiology of magenta tumours.
Occupation: Dye makers								
Chloroprene	Mouse Rat	Skin s.c., ingestion	Negative Negative	Lung Skin				Used only in the manufacture of artificial rubber. Structurally similar to vinyl chloride. Studies in man too limited to permit conclusions concerning carcinogenicity.

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B. Agents for which epidemiology or animal studies suggest carcinogenic potential

	ANIMAL STUDIES			CLINICAL AND EPIDEMIOLOGIC STUDIES				
Agent	Species	Route of absorption	Target organs and tissues	Route of absorp-	Latency (years)	Relative risk	Target organs and tissues	Comments
Occupation: Duprene makers; Neoprene makers; rubber makers								
Trichloroethylene	Rat Mouse	p.o. p.o.	Liver Negative	Lung Skin				No human studies available. Some 283 000 US workers exposed.
Occupation: Anesthetic makers; caffeine processors; cleaners; degreasers, disinfectant makers, dry cleaners, drug makers; dye makers; electronic equipment cleaners; fat processors; glass cleaners; mechanics; metal cleaners; oil processors; perfume makers; printers; resin workers; rubber cementers; shoe makers; soap makers; solvent workers; textile cleaners; tobacco denicotinizers; varnish workers								
Carbon tetrachloride	Mouse Rat Hamster	p.o., inhalation	Liver	Lung ?Skin				Positive dose-response relationship in mice. No epidemiologic studies available. Clinical reports of hepatomas following acute intoxication.
Occupation: Chemists, degreasers, fat processors; firemen, fluorocarbon makers; grain fumigators; ink makers; insecticide makers, lacquer makers, metal cleaners; propellant makers; chloroform makers; rubber workers; solvent workers, wax makers								
Acrylonitrile	Rat	p.o , inhalation	CNS, Zymbal gland, breast	Lung	20-25	3 (all sites)	Colon, lung	
Occupation: Acrylic fibre makers; fumigators; plastic product resin makers; textile workers								
Ethylene dichloride (1.2-	Rat Mouse	p.o. p.o.	Stomach, blood vessels, skin, breast Breast, uterus, lung					No human studies available. An estimated 5 million tonnes are produced annually in the US. About 2 million workers are exposed, including 34 000 with full-time occupational exposure (106).
Occupation: Adhesive makers; agricultural workers; Bakelite processors, camphor workers; chemical makers; dry cleaners; exterminators; furniture finishers; gasoline blenders; grain fumigators, insecticide makers, metal degreasers; ore upgraders; petroleum refinery workers, plastic workers; solvent workers; textile cleaners								
Mustard gas	Mouse	i.v., inhalation	Lung adenoma	Lung	10-25	37	Respiratory tract	Military exposures not associated with substantial risk of respiratory cancer.
Occupation: Japanese mustard gas workers								
Wood dust		s.c.	Local sarcoma	Lung	43 average (27-49)	500	Nasal cavity and nasal sinuses	Hardwood dusts.
Occupation: Cabinet makers, carpenters; furniture makers; instrument makers; sawmill workers; wood workers								
Leather dust				Lung	40-55	8	Nasal cavity and nasal sinuses	Carcinogen unknown.
Occupation: Boot and shoe manufacturers and repairs								
Arsenic	Mouse Rat	p.o. p.o.	Negative Negative	Lung Skin Oral	15-35	2.3-8	Lung Skin	Excess lung cancer has been reported in association with use and production of inorganic trivalent arsenic containing pesticides as well as metal smelting operations.
Occupation: Alloy workers; aniline colour makers; arsenic workers, Babbit metal workers, brass makers; bronze makers; ceramic enamel makers, ceramic makers; copper smelters, drug and dye makers; enamelers; fireworks makers, gold refiners; herbicide makers; hide preservers; insecticide makers; lead shot makers; lead smelters, leather workers, painters; paint makers; petroleum refinery workers, pigment makers; printers, printing ink workers; rodenticide makers, semiconductor compound makers; silver refiners; taxidermists, textile printers; tree sprayers; type metal workers, water weed controllers, weed sprayers								

TABLE VIII. .INDUSTRIAL AGENTS ASSOCIATED WITH CANCER

B. Agents for which epidemiology or animal studies suggest carcinogenic potential

	ANIMAL STUDIES			CLINICAL AND EPIDEMIOLOGIC STUDIES				
Agent	Species	Route of absorption	Target organs and tissues	Route of absorption	Latency (years)	Relative risk	Target organs and tissues	Comments
Chromium and chromates	Rat	Chromate pellets implanted in bronchi	Squamous and adenocarcinoma of the lung	Lung Skin Oral	21 average (10-30)	4-20	Lung Nasal sinuses	Excess risk of lung cancer was demonstrated in the chromate-producing industry, particularly during the 1930s and 1940s. Risk in other occupational settings with lower intensity exposures may not be substantially increased.
Occupation: Anodisers, copper etchers, electroplaters; gas workers, lithographers; metal workers, oil purifiers; photoengravers; photographers; process engravers; stainless steel workers; textile workers; welders								
Beryllium	Mouse, rabbit Monkey, rat	i.v. Inhalation	Bone sarcoma Lung	Lung	Lower limit of 10-15 years	1.3-2.0	Lung	The character of the work operation is particularly important-heating, surface grinding, machining, or any work that can produce fumes or finely divided dusts must be considered potentially hazardous. Three epidemiological studies have shown marginal excesses in relative risk. Further research is needed to clarify the relationship with duration and intensity of exposure, latency, and the contribution of pulmonary beryliosis and tobacco smoking history.
Occupation: Alloy workers and users (with aluminium, copper, nickel, and steel); electronic tube makers; fluorescent lamp makers (up until 1949); gas mantle workers; metallurgists; miners and extractors of ore (mainly beryl), nuclear reactor workers; plastic and ceramic workers; rocket and aerospace research workers								
Iron oxides (iron ore, haematite)	Hamster Mouse Guinea pig	Inhalation Inhalation Inhalation	Negative Negative Negative	Oral Lung	10+	2-5	Respiratory tract	Ingestion of dusts. Recognised excess risk of lung cancer confined to underground haematite Miners.
Occupation: Arc cutters; Bessemer operators; electric arc welders; flame cutters; friction saw operators, metalisers, seam welders; stainless steel makers; steel foundry workers								
Lead	Rat	p.o., parenteral	Kidney					No evidence for carcinogenicity in man. Carcinogenic doses of lead in animals far exceeds levels tolerated by humans.

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Agent	Species	Route of absorption	Target organs and tissues	Route of absorption	Latency (years)	Relative risk	Target organs and tissues	Comments
Occupation: Battery workers; brass foundry workers; ceramic makers; gasoline additive workers; glassmakers; imitation pearl makers, insecticide makers, lubricant makers; match makers; painters; plumbers, solderers; storage tank cleaners								
Nickel and compounds	Rat Rat	Inhalation i.m.	Lung Sarcomas		27 average (5-40) 23 average (10-40)	4.9-10.5	Lung	A number of animal inhalation studies using powdered nickel alone or with other inhalants such as nickel carbonyl vapor have been inconclusive. The risks of respiratory cancer have decreased significantly in workers first exposed since 1925, after which important preventive measures to reduce exposure to dusts and fumes were first implemented.
Occupation: Battery makers, ceramic makers; chemists, dyers; enamelers; foundry workers; gas platers; ink makers; magnet makers; Mond process workers; oil hydrogenators; organic chemical synthesizers; paint makers; petroleum refinery workers; spark plug makers; textile dyers, varnish makers								
Selenium and compounds	Rat	p.o.	Liver	Skin Lung Oral				No known carcinogenic effect in man. Protective effect against large bowel cancer has been proposed.
Occupation: Arc light electrode makers, copper smelters; electric rectifier makers; glass makers, organic chemical synthesizers; pesticide makers; photographic chemical makers, pigment makers; plastic workers, pyrite roasters; rubber makers; semiconductor makers, sulfuric acid makers, textile workers								
Ionizing radiation	Multiple	Irradiation	Skin, breast thyroid, bone, lung		2-25 15-25	3.7-5.5 1.1-3	Leukemia Epithelial tumours of other sites	Most leukemias are acute, some chronic myeloid.
Occupation: Aircraft workers; atomic energy plant workers; biologists; cathode ray tube makers; ceramic workers; chemists; dental assistants, dentists, dermatologists, drug makers; drug sterilizers, electron microscope makers; electron microscopists; electrostatic eliminator operators; embalmers; fire alarm makers; food preservers; food sterilizers; gas mantle makers; high voltage television repairmen, high voltage vacuum tube makers; high voltage vacuum tube users; industrialfluoroscope operators; industrial radiographers; inspectors using, and workers in proximity to, sealed gamma ray sources(cesium-137, cobalt-60, and iridium-192); Klystron tube operators; liquid level gauge operators; luminous dial painters,machinists; fabricated metal product workers; military personnel; nurses, oil well loggers, ore assayers; pathologists;petroleum refinery workers; physicians; physicists; pipeline oil flow testers; pipeline weld radiographers; plasma torch operators; plastic technicians; prospectors, radar tube makers; radiologists; radium laboratory workers, radium refinery workers, research workers; television tube makers; thickness gauge operators, thorium-aluminium alloy workers; thorium-magnesium alloy workers; thorium ore producers; tile glazers; uranium dye workers; uranium mill workers; uranium miners; veterinarians; X-ray aides; X-ray diffraction apparatus operators; X-ray tube makers								

	ANIMAL STUDIES			CLINICAL AND EPIDEMIOLOGIC STUDIES				
Agent	Species	Route of absorption	Target organs and tissues	Route of absorption	Latency (years)	Relative risk	Target organs and tissues	Comments
Non-ionizing radiation (Ultraviolet)	Mouse	Irradiation	Skin	Skin	5-50	2.5	Skin	Basal cell and squamous cell. Malignant melanoma.
Occupation: Agricultural workers; bacteriologists; bath attendants, beauty saloon workers; brick masons; cattlemen; chemists; construction workers, dentists, farmers; fishermen; food irradiators; gardeners; graphic illustrators; greenskeepers; horticultural workers; laboratory workers, lamp testers; landscapers; lithographers; lumberjacks; maintenance workers; meat curers; metal casting inspectors; microscopists, military personnel; movie projectionists; nurses, oil field workers; open-pit miners, opticians; optometrists; outdoor maintenance workers; paint and colour testers; paint curers, physicians, physicists; physiological optics workers; photo-bacteriologists; phototherapy technicians; pipeline workers; plasma torch operators, plastic curers; policemen (including crossing guards); postmen, printers, production workers in chemical processing; railroad track workers; road workers; seamen; ski instructors; space simulator workers; sportsmen; surveyors, textile inspectors; tissue culture workers; tobacco irradiators; vitamin D synthesis workers, welders, welder foremen, wood curers								
RADIOACTIVE ORES AND METALS								
Uranium/radon	Rat	Inhalation	Lung	Lung		10-38	Small cell carcinoma of the lung	Inhalation of radon daughters with irradiation of bronchial tree.
Occupation: Underground miners								
Radium				Oral	10-50	82 4	Bone sarcoma Leukemia and lymphoma Colon	Ingestion of radium-containing paint by women watch dial painters occurred up to about 1929.
Occupation: Luminescent watch dial painters								

Source - Schottenfeld & Haas, 1979. pp.156-169.

Answer 2

The information provided by this case series serves two epidemiological purposes. First it confirms the cases (a necessary first step in excluding the possibility of a pseudoepidemic, or cluster of diverse diseases which are not a single entity). Second, it identifies an unusual preponderance of oat cell cancers, and of cancers in relatively young workers (Table V). While oat cell cancer is not as uncommon as other sentinel tumours such as angiosarcoma or mesiothelioma, the finding of this proportion of oat cell cancers in a 'usual' series of lung cancers is highly unlikely.

Answer 3

Students may well observe that oat cell cancers comprise approximately 20% of all bronchogenic cancers, not the 9% stated here (Weiss, 1981). This is because the proportion of lung cancers due to small cell carcinoma has been increasing due to tobacco smoking, and has been found to be higher than the data suggested in 1971. They may also observe that the histological classification of cell type may not be comparable between the series under study, and that used in the comparison series.

Comparability of the classification schemes is clearly a prerequisite in interpreting whether the cell type observed in this series is actually different from that expected. These important questions about validity should take precedence over any discussion of how one computes the statistical significance of an observed difference.

Assuming that these questions have been resolved, however, one can estimate the probability (or improbability) that chance alone could account for this series using the formula for the binomial distribution. The binomial distribution permits the prediction of the probability of a given number of positive outcomes in a series (or specified number) of trials, when the outcome of each trial is dichotomous (+,-), and when the probability of a positive result on each trial is known. For example, first let us compute the probability, by chance, of observing exactly 12 cases of oat cell cancer among 14 lung cancers.

(a) The 14 cases of lung cancer can be seen as a set of N independent "trials". ($N=14$)
(b) Each trial (case of lung cancer) has the same probability "p" of yielding an oat cell (From Table VI, $p = 0.09$, or 0.1 for simplicity).
(c) Each trial also has the same probability "q", or $1-p$ of not yielding an oat cell cancer ($q = 1-0.1 = 0.9$)
(d) The total number of oat cell cancers that would occur in a set of N trials, if such a set of trials were repeated infinitely, is a variable called "X", and X is distributed binomially. Symbolically

$$X \quad B(P,N)$$

(e) The letters "p" and "N" indicate that the shape of any particular binomial distribution will depend upon the two parameters p (here $p=0.1$) and N (here $N=14$). B indicates that X is distributed binomially as a function of p and N.
(f) Since in this series of 14 lung cancer cases there were observed 12 oat cell cancers, here $X=12$.

(g) To calculate the probability of observing exactly 12 oat cell cancers in a set of 14 trials, repeated infinitely, the following formula should be used:

$$\text{Prob. }(X=12)= \frac{N!}{X!\ (N-X!)}\ p^{X}\ q^{N-X}$$

$$= \frac{14!}{12!\ (14-12)!}\ (0.1)^{12}\ (0.9)^{(14-12)}$$

Where $N=14$
$X=12$
$p=0.1$
$q=0.9$
$14!=(14)x(13)x(12)..(1)$

$$\text{Prob }(X=12) = 7.37\ x10^{-11}$$

While this extremely small number tells us the probability of observing exactly 12 oat cell cancers, it must be added in the probability of events which are even more extreme than that observed. In this case, the probability of observing 13, and 14 cases of oat-cell cancer in the series of 14 lung cancers must be computed. These are then added to the probability of observing exactly 12 cases. Thus:

Probability of exactly 13 cases equals--

$$\text{Prob. }(X=13)= \frac{N!}{X!\ (N-X!)}\ p^{X}\ q^{N-X}$$

$$= \frac{14!}{13!\ (14-13)!}\ (0.1)^{13}\ (0.9)^{(14-13)}$$

Where $N=14$
$X=13$
$p=0.1$
$q=0.9$

$$\text{Prob }(X=13) = 1.26\ x10^{-12}$$

Probability of exactly 14 cases equals--

$$\text{Prob. }(X=14)= \frac{N!}{X!\ (N-X!)}\ p^{X}\ q^{N-X}$$

$$= \frac{14!}{13!\ (14-13)!}\ (0.1)^{13}\ (0.9)^{(14-13)}$$

Where $N=14$
$X=13$
$p=0.1$
$q=0.9$

$$\text{Prob }(X=14)= 1\ x10^{-14}$$

Thus, the probability of observing 12 or more oat cell cancers in this series of 14 lung cancers, by chance alone equals 7.497×10^{-11}.

Use of the binomial has simply allowed us to quantify what was intuitively obvious, even without statistical testing. This technique would be more useful if it were applied when the series of cases first began to accumulate, allowing early recognition of a problem.

Answer 4a

Without belabouring the arithmetic, a similar approach could have been used to quantify at what point the accumulating series became improbable. Thus--

Answer 4b

When the first case of lung cancer appeared, the probability of observing one oat cell was

$$\text{Prob. }(X=1) = \frac{N!}{X!\,(N-X!)}\,p^{X}\,q^{(N-X)}$$

$$= \frac{1!}{1!\,(1-1)!}\,(0.1)^{1}\,(0.9)^{(1-1)}$$

Where $N=1$
$X=1$
$p=0.1$
$q=0.9$

Prob. $(X=1) = 0.1$

(However, the first case of lung cancer did not happen to be an oat cell carcinoma.)

When the second case of lung cancer appeared, the probability of observing exactly one oat cell cancer was 0.18, the probability of observing two oat cells was 0.01, and the probability of observing at least one was 0.19.

When the third case of lung cancer appeared, the probability of observing exactly two oat cell cancer was 0.0135, the probability of observing three oat cells was 0.001, and the probability of observing at least two was 0.0145.

While tedious, this exercise shows us that, based upon what was known about the distribution of cell type in 1971, this series of lung cancers became improbable in 1962. Even if oat cell cancer had comprised 20% of all lung cancers at that time, the series would still have become improbable after the fourth case. Early recognition of a problem would have been a first step towards public health intervention.

Answer 5

The toxicological studies indicate that BCME has induced cancer in two species of animals by two routes of exposure. In addition, there was an apparent cluster of lung cancer among workers at the plant, even if the unusual distribution of cell type had yet not been noticed. Although in 1971, the chest physician was just beginning his study, and the company had not yet published an internal prospective epidemiological study of lung cancer incidence from 1964 to 1967 at the plant, the evidence still suggests that BCME should be treated as a presumed human carcinogen (Figueroa, et al. 1973). Sound public health practice would require that the scientific and regulatory community be notified and that a variety of control measures should be introduced at once. These include substitution of a less toxic chemical (if one exists), complete engineering enclosure of the process, and reduction of exposures through ventilation. Other chemical companies which produce or use chloromethyl methyl ether and have potential exposure to BCME should be notified. All of these measures should be undertaken even while the remaining scientific uncertainties are being elucidated. Otherwise, the delay needed to increase scientific certainty will lead to the unnecessary exposure of more workers.

Answer 6

Two separate issues are involved in answering this question. First, has sufficient time elapsed since the initial exposure of these workers, so that the outcome (here cancer) is likely to appear? Second, given the frequency of disease occurrence, has there been a sufficient number of person-years at risk, so that the study will have adequate statistical power?

The first question depends on the length of the induction latency period for this particular cancer. While this could best be estimated from the data from the CMME plant (which cannot actually be determined from the paper of Figueroa, et al. 1973), one could assume that at least 15 years are usually necessary for lung cancer to become evident. Thus the observation period from 1955-1972 will be shorter than this for most of the cohort.

Answer 7

The four variables which one must specify in order to calculate power are:

(a) Alpha error = the probability, by chance, of observing a statistically significant effect when in fact none exists;

(b) The magnitude of the true underlying effect that one wishes to be able to detect;

(c) The incidence rate (or incidence density) among the unexposed comparison population; and

(d) The number of person years at risk among the exposed.

In practice, factor (a) is usually set by convention at 0.05. Also, factors (c) and (d) are usually combined into a single variable which is the number of 'expected cases'. Estimating the number of expected cases is not a simple matter, since it is a function of both the age-specific incidence rates for the disease under study, and of the age distribution of the person-years at risk.

Answer 8a

It is clear from the figure that statistical power increases both as the number of expected cases increases, and as the hypothesized underlying rate ratio increases. Conversely, statistical power decreases with a smaller number of expected cases (either because the disease is rare, or because the number of person-years at risk is small) and as the assumed underlying rate ratio decreases.

Answer 8b

Given that 0.49 cases are expected, the statistical power of the study would be approximately 15% (14%) for an underlying rate ratio of 2.0, approximately 50% (53%) for a rate ratio of 5.0, and approximately 90% (92%) for a rate ratio of 10.0. (Note- statistical power can be determined exactly either by using a number of computer programs, by consulting a statistician, or by using the formula given by Beaumont & Breslow, 1981, and their tables of the Z distribution. This exercise will not attempt to teach the mechanics of computation.)

Answer 9

There are several options which should be considered. If another large plant could be identified which has equivalent levels of BCME exposure, then the study might better be done there. Alternatively, if several small plants can be found, these might be combined to obtain a larger study population. The two other possibilities are to cancel the study, or to conduct it despite the low statistical power, assuming that the large apparent excess observed in the previous plant (also involving a small workforce) suggests a large underlying effect. The drawback with the last approach would be that a negative study would be quite unconvincing.

SPECIAL DIRECTIONS TO INSTRUCTORS

This case is one of the more difficult of the series. In particular, questions 3, 4, and 7 are best understood by audiences who have completed at least an introductory course in biostatistics. Because the important part of the case involves the principles, rather than the arithmetic, however, it is still suitable for classes with less statistical training if the discussion is directed towards these underlying concepts. We suggest that instructors should not expect participants to work through any of these calculations during the discussion. Rather, they they should consider distributing the instructors notes for the students to take home and to review later.

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E

URINARY SYMPTOMS IN POLYURETHANE FOAM WORKERS*

PART 1

On 28 March 1978, a local board of health in a small town received a telephone call from an emergency-room physician in a nearby community hospital. The physician reported that 11 workers from the same polyurethane foam factory had come as a group to the emergency room at 9 A.M. that Monday morning. All of the workers had complained that they had trouble urinating, although each of them had produced a normal urine specimen.

Question 1

If you were on the staff of the local health department, what would you do to pursue this report?

PART 2

The eight men and three women, who had sought medical attention, had suffered for several months from difficulty in starting their urine stream, which was weak and difficult to maintain. The plant manager confirmed that many more employees had similar problems and that two employees had had surgery for inability to urinate. He wanted to cooperate in every way since his earlier efforts to have the bathrooms cleaned and inspected had not solved the problem being experienced by employees.

The factory manufactured polyurethane foam seats for automobiles. The plant had two parallel production lines, as well as finishing, supply, storage, laboratory, and clerical areas. At the head of each production line, the ingredients of the foam were compounded: toluene diisocyanate, polyols, fire retardants, and a catalyst. This mixture was poured into open waxed molds, and a cover was placed on top of the mold as the foam expanded. The closed mold was then passed through an oven, after which the cured foam cushion was removed and conveyed to the adjacent finishing room. There, the foam was trimmed, inspected, and bagged in polyethylene for shipping. The mold and its cover were stripped of excess foam, sprayed with wax, and fitted with nets and wires for the structural support of the next cushion.

The major building block of polyurethane is toluene diisocyanate (TDI), which causes occupational asthma in a small percentage of workers who become sensitized, and which may cause excessive decrements in lung function in non-sensitized workers, comparable in magnitude to the yearly decrement caused by cigarette smoking (Diem, _et al_. 1982). Neither TDI nor other chemicals used in the plant were known to cause urinary symptoms. However, since a large number of employees seemed to have similar urinary complaints, further investigation was warranted.

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* By Kathleen Kreiss, 1982; revised 1985.

Question 2

How would you investigate this apparent outbreak?

PART 3

The only new chemical which had been introduced in the preceding year was a catalyst, dimethylaminopropenenitrile (DMAPN). The catalyst was introduced on one production line in August 1977 and was used irregularly until December of that year. From December 1977, both assembly lines had used the catalyst. Since DMAPN was a leading suspect for a chemical culprit, the management removed it from production on 29 March 1978.

An epidemiological survey was started a week later. All available employees completed a questionnaire and gave a urine sample for urinalysis and a blood sample. A case of bladder dysfunction was defined as an employee who had experienced any two of the following four symptoms: hesitancy, straining to void, decreased force of the stream, or increased duration of urination.

Question 3

a) Why was a case definition made?

b) Who were the controls?

PART 4

104 of the 208 employees met the case definition. The attack rate among the 166 persons exposed to DMAPN in the production or finishing areas was 63%. No cases occurred among the remaining 42 employees. There were 20 cases (55.6%) among 36 exposed women and 84 cases (65.5%) among 130 exposed men. Attack rates did not increase with age.

Persons classed as cases had a variety of symptoms listed in Table VIII. Patients complained of having to press on the lower abdomen to initiate urination. Several persons volunteered that they lost the urge to urinate and voided once a day or by habit. Others described increased frequency of urination, particularly as their conditions improved. Some lost urethral sensation or, as their conditions improved, had urethral burning. The majority had vague abdominal discomfort that they did not associate with bladder distension. Sexual difficulties occurred in 23 persons classed as cases and six non-cases. Thirteen cases had upper extremity numbness.

Question 4

a) What might be the mechanism of this set of complaints? How would you confirm your hypothesis?

b) What is the design of this study, case-control, cohort, or other?

Table VIII. Frequency of urinary complaints; foam plant in Massachusetts, 1978.*

Symptoms	Cases	Noncases
Increased duration	102/104	1/104
Hesitance	98/104	0/104
Need to strain	98/104	0/104
Decreased stream	94/104	4/104
Subjective retention	70/102	4/104
Dysuria	70/104	13/104
Abdominal discomfort	61/103	6/104
Urgency	47/104	3/104
Decreased frequency	47/104	23/104
Increased frequency**	44/104	23/104
Urethral discharge	19/104	2/80
Nocturia	15/104	10/104
Gross haematuria	12/104	4/104

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* Source - Kreiss, K. et al. 1980, Table VIII. p 742.

** Includes eight cases reporting decreased frequency as well during a portion of their illness.

The epidemic curve is shown in Figure 3. Three cases of bladder dysfunction occurred among the second-line workers in the three months before using DMAPN in that production line.

Question 5

What do these three cases suggest about the route of exposure?

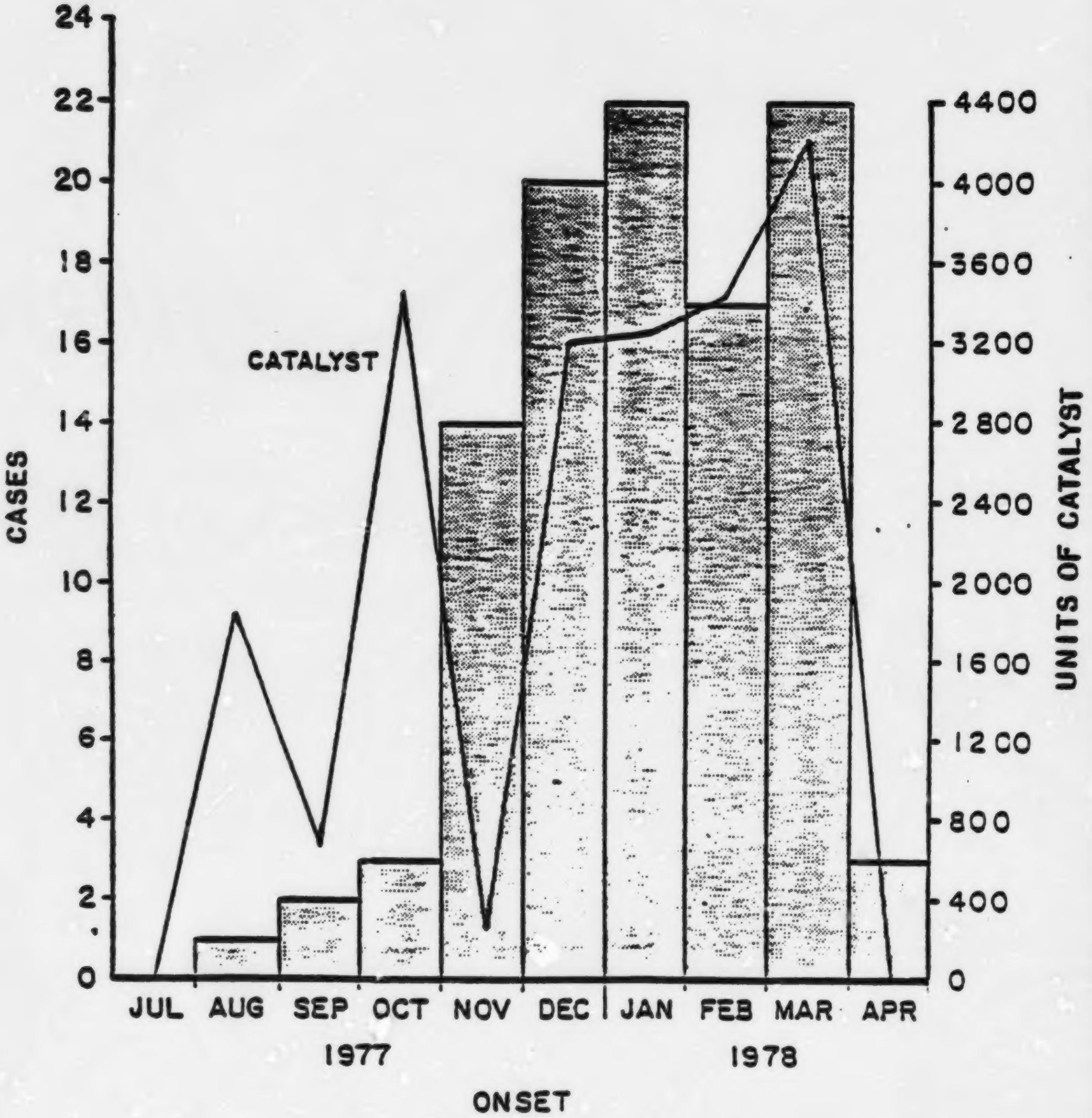

Fig. 3. Cases of bladder dysfunction in plant workers, by month of of onset and amount of DMAPN catalyst used, July 1977 to April 1978. (Source - Kreiss, K., *et al*. 1980. Fig. 1. p. 743).

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Question 6

Does the epidemic curve support the suspicion that DMAPN caused the outbreak of bladder dysfunction? What other information would be helpful?

Figure 4 presents cumulative incidence rates for diverse job categories. Figure 5 presents data by shift. Production was higher on the second and third shifts, because no production innovations were done during those shifts (Table IX). In addition, the second and third shifts were exposed to more scrap and waste foam on the floor because a clean-up was deferred to the third shift.

Question 7

How might you explain the case rates by shift?

Question 8

Having concluded the epidemiological survey, what would you do next?

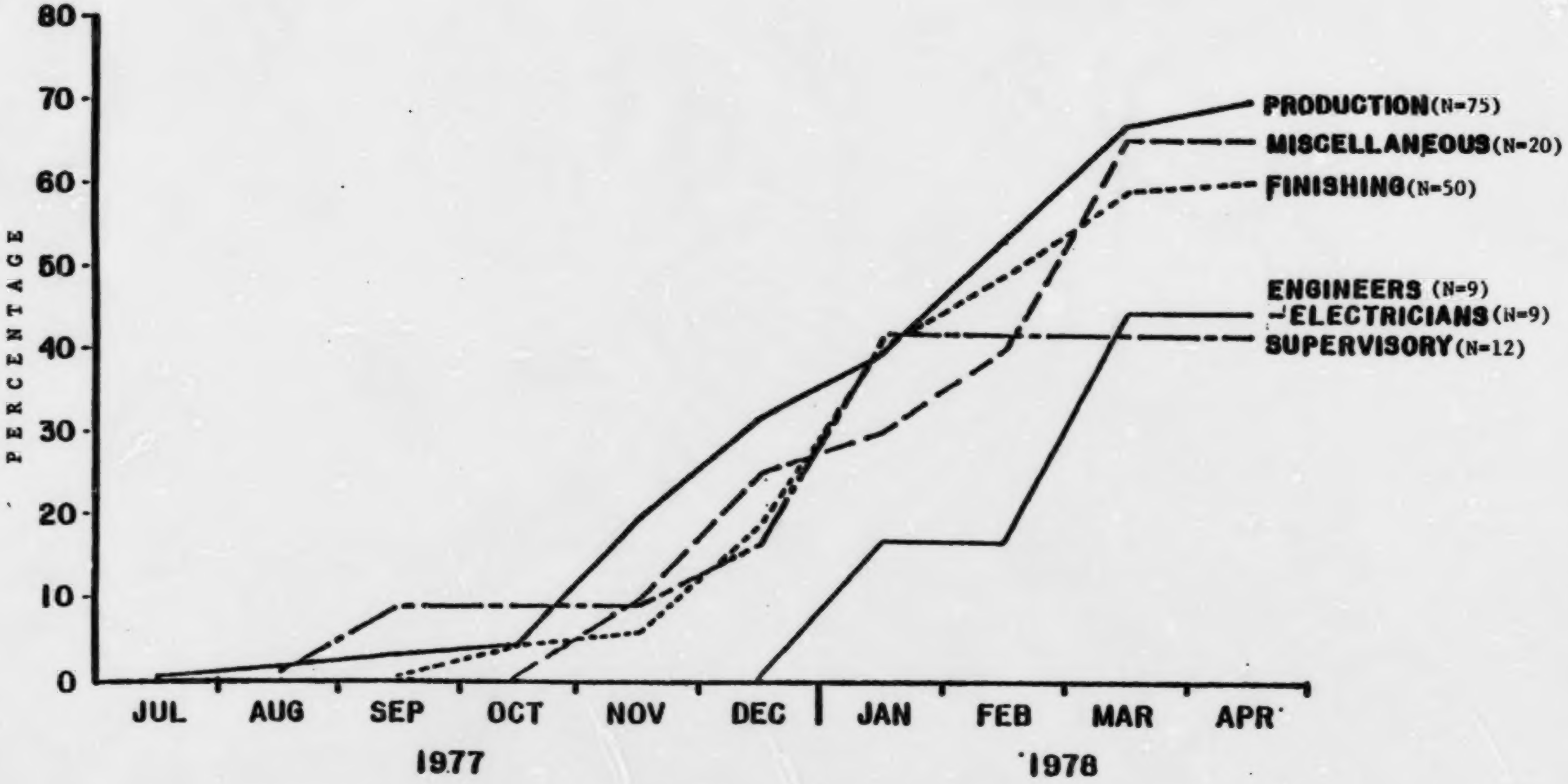

Fig. 4. Cumulative percentage of plant workers having bladder dysfunction, by month and work category, July 1977 to April 1978. (Source - Kreiss, K., et al. 1980. Fig. 2, p. 743).

E 6

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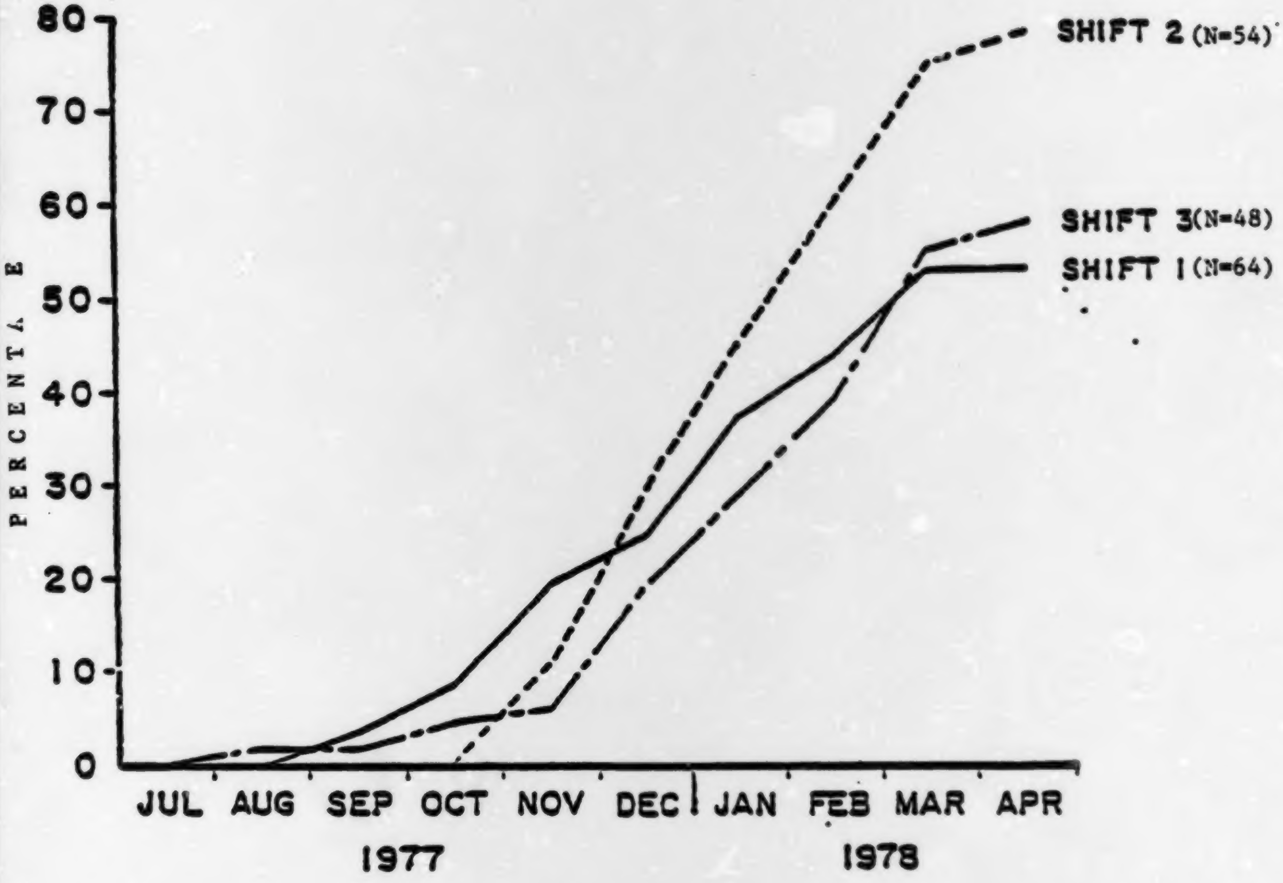

Fig. 5. Cumulative percentage of plant workers at risk having bladder dysfunction, by month and shift, July 1977 to April 1978.

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Table IX. Catalyst-containing foam produced and scrapped by line and shift.

	Shift 1	Shift 2	Shift 3	Total
	Produced 13-29 March 1978 (in kg)			
Line 1	23 381	23 986	26 190	73 537
Line 2	13 659	14 073	16 123	43 855
Total	37 020	38 059	42 313	117 392
	Scrapped in February and March 1978			
Line 1	8 372	6 262	7 529	22 164
Line 2	3 277	1 957	2 816	8 050
Total	11 650	8 219	10 345	30 214

PART 5

An outbreak of bladder symptoms occurred in a polyurethane foam plant in Maryland in the same time period and was investigated with similar results (Keogh, et al. 1980). In total, at least five foam plants were found to have had epidemics of bladder neuropathy before the use of DMAPN catalyst was discontinued. The sole producer, Union Carbide, had never observed this occupational illness among its employees. In addition, DMAPN had been used as a catalyst for more than 20 years without an apparent problem, in acrylamide grouting used in mining and tunnel construction.

Question 9

a) How might you explain the delay in recognizing DMAPN as a neurotoxin?

Union Carbide had a material data safety sheet on their product reproduced below. NIAX Catalyst ESN is the trade name for the catalyst which consisted of 95% DMAPN and 5% of bis (2-dimethylaminoethyl) ether.

b) What are the limits of testing LD 50's? How would neurotoxicity be recognized if toxicologic testing included only this battery of tests? Do you know of other workplace epidemics of neurological disease?

SAFETY DATA SHEET: Niax catalyst ESN

This is a summary of single exposure studies on animals. The data indicate the relative degree of hazard in handling the product. Increasing degrees of hazard are expressed by these terms: slight, moderate, definite, serious. it must be remembered that results of experiments on animals cannot be numerically translated to probable human response.

The US National Research Council defines toxicity as the capacity of a substance to produce injury. Hazard is the probability that injury will result from the handling or use of the substance in the quantity, frequency and manner proposed.

Toxicity is only one factor important in determining the degree of hazard in handling a chemical or in a proposed use. Physical properties of the chemical together with extent and frequency of exposure are equally important.

The term LD_{50} has been adopted as a uniform expression of single dose toxicity for comparing one chemical with another. It refers to that quantity of chemical which kills 50% of exposed animals. For further uniformity, quantities are expressed in grams or mililitres of chemical per kilogram of animal body weight.

Single skin penetration refers to a covered 24-hour skin contact with the liquid chemical.

Single inhalation refers to continuously breathing a certain concentration of chemical vapours for a specified period of time.

Primary irritation refers to the skin response following uncovered skin contact. A covered contact can be expected to have a more severe effect.

Eye injury refers to surface damage produced by contact of the eye with the chemical.

Legal responsibility is assumed only for the fact that all studies reported here, and all opinions, are those of qualified experts.

Single oral dose to rats: Moderate hazard

LD_{50} - 2.46 ml per kilogram body weight.
For comparison a 10% solution of acetic acid has an LD_{50} of 3.53 gm/kg.

Single skin penetration in rabbits: Definite hazard

LD_{50} - 0.445 millilitres per kilogram body weight.
This result suggests that skin penetration in harmful amounts may occur after moderate contact in terms of skin area involved and duration of contact. Skin contact is to be avoided.

Single inhalation by rats: Moderate hazard

Rats were not killed by an 8 hour exposure to substantially saturated vapours in room air. However, these concentrated vapours caused irritation of eyes, lower legs and feet.

Skin irritation: Slight hazard

The undiluted chemical caused no reaction on the tender skin of the rabbit belly greater than a faint redness of short duration.

DOT - 4 hour covered patch test - not a corrosive.

Eye injury: Serious hazard.

A 15 % solution was the least concentration causing significant injury in the rabbits' eye.

This chemical is a serious eye injurant. Eye protection should be worn when handling. A physician should see all cases of eye contact as soon as possible after a 15-minute emergency eye washing is completed.

Repeated human patch tests made on 50 human volunteers using a polyether foam catalyzed with Niax Catalyst ESN was not an irritant or sensitizer.

INSTRUCTOR'S NOTES
URINARY SYMPTOMS IN POLYURETHANE FOAM WORKERS

Summary

This case illustrates how to recognize and investigate (using cross-sectional techniques) an outbreak of autonomic neuropathy. It provides a useful example to discuss two considerations in data analysis: 1) How best to analyse prevalence data, and 2) What are the implications of reducing a large number of related symptoms or signs into a single dichotomy of case versus non-case. Like the study on the neurological symptoms produced by methyl butyl ketone (p. cl), it demonstrates that the traditional methods of outbreak investigation can successfully identify the causal agent when the disease under study is rare, and when latency is short.

PART 1
Answer 1

The information given is not sufficient to make a medical diagnosis or to relate the workers' complaints to a workplace exposure. To verify the complaints, the available medical and demographic information must be collected. This is most easily accomplished by reviewing the medical records of the workers who were seen in the emergency room. These records contain age, sex, complaints, results of physical examination and laboratory evaluation of urine and other biological specimens, and identity of patients, should further information be required. In addition, some information might be available about whether the complaints stemmed from an acute process, with 11 employees being affected simultaneously and coming as a group from work; or alternatively, from a chronic condition, in which case the implications of 11 persons meeting as a group at the emergency room after a weekend's respite are different. In fact, the latter was the case, and many more employees than 11 had agreed to meet at the hospital. They wanted to dramatize the work-related character of their complaints, which had been ignored by private physicians whom they had consulted individually.

In addition to ascertaining more about the medical aspect of the workers' complaints, information must be sought about the work environment of the polyurethane foam plant. This information can be sought from the patients and from the management. The factory management may be able to confirm whether there is an epidemic in the workplace based on absenteeism or complaints to a medical department (if any). The management is usually the only source of a list of workplace chemicals and a detailed account of changes in production process, ventilation, and industrial hygiene measurements of workplace exposures.

Most sanitarians and other small town health departments do not have training in occupational health. In fact, the sanitarians in this health department had received a request for assistance from the factory manager several months before and had inspected the toilets of the factory, which were found to be in a sanitary condition. This question provides an opportunity to discuss the resources available to those nonspecialists faced with occupational health problems, be they sanitarians, physicians, nurses, or workers.

In the USA, occupational health expertise exists in schools of medicine and public health and in governmental agencies concerned with health or labour at state and federal levels. In the case presented here, the local board of health contacted the Massachusetts Occupational Hygiene Physician, who in turn involved the Harvard School of Public Health, the National Institute for Occupational Safety and Health (a non-regulatory health research agency), and the Occupational Safety and Health Administration (a regulatory agency in the US Department of Labor). This discussion of resources and expertise for occupational health investigations might include the strengths and limits of each, including which groups have authority to enter workplaces.

PART 2
Answer 2

Three simple means of investigation exist for characterizing an outbreak of a new occupational disease: an epidemiological survey, referral of severely affected persons to medical specialists for detailed diagnostic testing, and correlation of changes in production processes or measurements of chemical exposure with the occurrence of illness.

The goals of an epidemiological survey are to establish who is affected, where in the production process, and when. Characterizing who is affected requires questions concerning age, sex, job category, personal hygiene, shift worked, duration of employment, absenteeism, and presence of specific symptoms. A case definition must be formulated for the purpose of comparing affected employees (cases) with unaffected employees (controls) for attributes or risk factors for illness. Locating onset of complaints in time may also give a valuable clue to which changes in production processes may be responsible. Latency of the illness after first exposure to the plant might be determined by analysis of the symptom experience of recently-hired employees.

Appropriate diagnostic testing, in conjunction with a questionnaire survey or by referral to medical specialists, requires hypotheses about the nature of the disorder. In this outbreak, the investigators were puzzled because the emergency-room physician had made no diagnosis and the available data were not compatible with infection or prostatic obstruction especially considering that some of those effected were women.

No known industrial chemical produced urinary retention on a pharmacological basis and persons complained of symptoms persisting over a week-long plant closure during a blizzard. No known neurotoxin affected the bladder preferentially. It appeared that detailed testing by neurologists and urologists was the most promising line. Another group of investigators chose to do intravenous pyelograms as well to evaluate the disorder (Keogh, et al. 1980). Of course, hypotheses about the nature of the illness must be formulated before the design of the symptom portion of the questionnaire.

Production records were useful in several ways. We reviewed whether any new chemicals had been introduced in the preceding year and where and in what amount they had been used. We were also interested in production figures by shift and by assembly line.

PART 3
Answer 3

a) In this setting the assessment of disease status must be based on a variety of symptoms, which should be condensed into a single summary variable as to whether each individual was ill or well. A case definition, which is to a large extent arbitrary, is one method for doing this. This approach allows us to divide the population into cases and non-cases, or controls, in order to look for differences in characteristics which may be valuable clues as to risk factors or protective factors for disease. Had our investigation measured some quantitative measure of dysfunction, we might have chosen to retain the continuous data in our analysis.

b) Non-cases could serve as controls. However, another approach to the data analysis was to divide the factory population into an "at-risk" group and an unexposed group. The at-risk group included all employees who worked in the production or finishing areas, who were assumed to be exposed to DMAPN. These at-risk employees were compared with employees working in nonmanufacturing areas such as the warehouse. This means of analysis is that of a cohort study, rather than a case-control study. Both means of analysis use a comparison group, or control group. In a cohort study, the exposed group is compared to the unexposed group for disease outcome. In a case-control study, the case group is compared to the non-case group for risk factors.

PART 4

Answer 4

a) Occupational neuropathies which affect the peripheral nerves usually cause numbness or tingling (sensory changes) or weakness (motor changes) in the hands or feet. The bladder nerves are part of the peripheral nervous system, but are autonomic rather than somatic. Some toxic neuropathies have autonomic effects. For example, acrylamide causes abnormal sweating. Although only a small number of persons (13/104) complained of extremity numbness, suggesting a peripheral neuropathy, the mechanism of the urinary and sexual dysfunction was undoubtedly neurological. A sensory neuropathy was suggested by abnormal urethral sensation and loss of the sense of bladder fullness. A motor neuropathy was suggested by the difficulty in initiating and maintaining the urine stream.

Eight symptomatic employees were referred for neurologic testing two and a half weeks after DMAPN was removed from production. Seven of them had neurological abnormalities of the distal lower extremities on physical examination. Nerve conduction tests on peroneal and sural (lower leg) nerves and on pudendal nerves showed at least one abnormal measurement in four of the eight. Five patients lacked the detrusor reflex which empties the bladder in a coordinated fashion. Two additional patients had a high sensory threshold for bladder filling. These findings on neurological testing and cystometrograms are consistent with a neuropathy affecting the bladder nerves.

b) In this study, prevalence information was collected from 208 of 213 current workers. Five workers refused to participate. Because the information on exposure and disease was collected simultaneously, this study is cross-sectional. Only by chance do the number of cases (104) equal the number of non-cases.

Optionally, the instructor can discuss selection of the appropriate analysis. The appropriate analysis is calculation of exposure specific prevalence rates and prevalence ratios. In this study the alternate approach, the calculation of the odds ratio, is a poor approximation of the prevalence ratio, probably because these data do not meet the caveat that the disease prevalence must be low (less than 10%) for the odds ratio to approximate the prevalence ratio.

DATA

	Case	Not Case	
DMAPN +	104	62	166
DMAPN -	0	42	42
	104	104	208

$$\text{Prevalence ratio} = \frac{\frac{104}{166}}{\frac{0^*}{42}} = 26.3$$

$$\text{Odds ratio} = \frac{\frac{104}{0^*}}{\frac{62}{42}} = 70.4$$

*Assume 1 for purposes of ratio calculation

Answer 5

The route of exposure was probably inhalation. Handling foam was not specifically associated with the bladder syndrome. In addition, there were cases among persons who infrequently handled foam or chemical compounds, e.g., electricians. Differences for cases were not observed in handwashing practices, location of eating, or showering after work. Unpublished animal data suggest absorption by both skin and respiratory routes.

Answer 6

A rough exposure-response relation is suggested by the amount of catalyst used in monthly production and the incidence of new cases. The outbreak appears to have abruptly stopped by the time of the questionnaire survey in the second week of April 1978. Exposure-response relationships are an important finding in support of causal association. In this plant, production varied by shift. Thus, case rates might be expected to vary by shift, in line with production. In addition, exposure probably varies by job category.

Answer 7

The case rates presented in Fig. 5 are 78% for the second shift, 58% for third shift, and 53% for first shift. Table IX indicates that second and third shifts each had higher production. What is not supplied to the student is a characteristic that is associated with exposure: absenteeism. Absenteeism is often high for persons working from 23h00 until 07h00 . When case rates are calculated for person-months of exposure, second and third shift had nearly equal case rates (0.14 and 0.15 cases per person-month, respectively), and they were double the case rate for the first shift (0.07 cases per person-month). The case rates by shift, adjusted for absenteeism, support an exposure-response relation between DMAPN and rates of bladder neuropathy (Table X).

Another useful investigation might be a study of differences in ventilation by shift.

Table X. Absenteeism among employees in production work.

	Dec.	Jan.	Feb.	Mar.	Total
Shift 1					
Precentage absent*	5.3	8.0	5.1**	4.1	5.5
Average present/day	46.0	43.3	47.9	47.6	46.3
Shift 2					
Precentage absent*	3.9	5.2	6.7**	4.2	4.8
Average present/day	43.9	44.3	43.5	43.7	43.7
Shift 3					
Percentage absent*	8.6	9.3	6.4**	9.2	8.5
Average present/day	41.8	43.1	48.4	46.7	44.9
Total					
Percentage absent*	5.9	7.5	6.0**	5.9	

*Percentage absent--Number of persons absent x number of days of absence/Total person days.

**Excluding February 1978 blizzard.

Answer 8

There are many appropriate next steps:

a) Air measurements of DMAPN were attempted ten days after the catalyst was withdrawn from production, and DMAPN was detected at 0.11 mg/m^3. However, since there were no environmental measurements while DMAPN was used in production, the quantitative exposures associated with this epidemic are unknown.

b) A scientific and ethical responsibility is to see whether this epidemic was repeated elsewhere. The scientific responsibility illustrates another criterion for causality in epidemiological association: consistency of findings among investigators. This epidemic was a newly described association of a chemical exposure with a new kind of neuropathy. Another group of investigators had similar findings in a polyurethane foam plant in Maryland (Keogh, et al. 1980). In the absence of a known similar outbreak, other users of the chemical can often be identified through the producer or with the assistance of governmental authorities (in the USA, the Occupational Safety and Health Administration or the National Institute for Occupational Safety and Health).

c) Prevention of further cases of an occupational disease is the justification of all the investigative steps. When the cause of an outbreak of occupational disease is clear, control of the disease is usually clear. In this instance, the outbreak was terminated rapidly when the catalyst was removed from production. The producer, Union Carbide, voluntarily stopped selling the catalyst. In other instances, engineering controls and personnel protective equipment might be appropriate preventive measures, if substitution of chemical catalysts had not been possible. In that instance, animal toxicological studies might be needed to determine safe levels of exposure.

d) Follow-up of persons classed as cases is important to determine the natural history of the disease and the efficacy of any treatment. In this outbreak, 51% of the cases noted symptomatic improvement at the time of the survey (which was 8 to 13 days after removal of DMAPN from production). An additional 21% of the cases said they were back to normal. Three months later, 76% of the previous cases were asymptomatic, and the remainder reported improvement. However, some abnormalities were present at two-year follow up in latter group (Bakers, et al. 1981).

In the case of some industrial neurotoxins, treatment may be efficacious. For example, physicians try to accelerate the excretion of lead with disodiumedetale and of chlordecone (Kepone) with cholestyramine. The neurological effects of carbon monoxide poisoning are treated by the administration of oxygen. Unfortunately, for most occupational neuropathies caused by chemicals there is no known treatment.

Answer 9

a) Even in a epidemic situation with 104 cases, the etiology of complaints was not discovered for several months. In this outbreak, more than half of the persons classed as cases had seen physicians without diagnosis, improvement, or the physician notifying the public health authorities or occupational medicine specialists. As described above, a group of symptomatic persons chose to dramatize the work-related character of their disorder by going as a group to an emergency room. The plant manager had attempted to get public health assistance, but the local health office was unaware of more expert resources or the possibility of a new occupational disease. That five outbreaks occurred, only two of which were investigated, is a commentary on the awareness of occupational health by the physician community.

The grouting industry had used DMAPN as a catalyst in the polymerization of acrylamide, also a neurotoxin. In fact, the first case report of acrylamide neuropathy in 1967 had simultaneous exposure to DMAPN. The use of the catalyst in the grouting industry was characterized by outdoor location and by exposure of only a few persons at one time. Both of these factors may explain why bladder neuropathy cases may not have occurred or been recognized. Males with the symptoms of bladder neuropathy would probably be diagnosed as having prostate conditions.

In summary, an epidemic involving large numbers of men and women, indoors in a factory situation, was a prerequisite to making the association between DMAPN exposure and a new kind of neuropathy. Even then, the diagnosis was not speedy or automatic.

b) The LD_{50} gives no information regarding the mechanism of toxicity. However, the data safety sheet does suggest that the chemical is absorbed by cutaneous and respiratory routes. One might question what was meant by the statement "concentrated vapours caused irritation of eyes, lower legs and feet": did inhalation cause a peripheral neuropathy of the lower limbs of rats? No routine testing for neurotoxicity is customary for industrial chemicals. Indeed many neurotoxins have been discovered because of workplace epidemics: acrylamide, n-hexane, methyl n-butyl ketone, chlordecone, and leptophos. Routine neurotoxicologic testing of chemicals is limited in part because of the lack of well-developed methodology. For an excellent overview of chemical neurotoxins, see Spencer & Schaumburg (1980).

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GYNAECOMASTIA IN ESTROGEN EXPOSED WORKERS*

PART 1

On 26 April 1976, the Secretary of Health for the Commonwealth of Puerto Rico, contacted the Epidemic Intelligence Service (EIS) Officer, Environmental Hazards Activity, Cancer and Birth Defects Division, Bureau of Epidemiology, US Center for Disease Control (CDC), Atlanta, to request assistance in evaluating the health of workers at a pharmaceutical company in Puerto Rico. The plant manufactured contraceptive pills and the Secretary had received complaints of menstrual disorders in approximately 50% of the 100 female employees, as well as complaints of possible estrogenic effects in some male employees. Further discussions involved other members of the Bureau of Epidemiology as well as the Hazard Evaluation and Technical Assistance Branch, NIOSH, Cincinnati. It was agreed that a combined NIOSH-CDC investigation should be conducted. Accordingly, the EIS officer and an epidemiology elective student were despatched from Atlanta to San Juan on 28 April 1976.

Question 1

a) An investigation undertaken by a dual agency approach to a Spanish speaking area raises a number of organizational difficulties. How would you attempt to avoid chaos?

b) What information would you have requested initially to decide if a study was indicated and feasible?

PART 2

The following is a description of the plant:

The factory occupied a coastal site at Dorado, 15 km west of San Juan, and formed one of a group of new enterprises attracted to Puerto Rico from mainland USA by financial incentives and the ready availability of labour. The plant was built two years prior to the investigation, and had been fully operational for less than eighteen months. It employed 57 employees in two shifts, all but one of whom were Puerto Rican.

All the ingredients of the oral contraceptive pills were imported from mainland USA and the flow of materials through the plant began at the warehouse . In essence, the flow through the plant was thereafter clockwise. Quality assurance inspection was undertaken on samples of the batches of raw materials before the shipment was cleared for weighing. The inert fillers and lubricants were weighed by a technician wearing gloves and a NIOSH respirator approved for nontoxic dust in an area supplied with local exhaust ventilation.

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* By J.M. Harrington, 1983; edited July 1985.

The active ingredients - mestranol and norethindrone - were added to the inert mixture in the granulation room. The estrogen was added dissolved in methanol. After mixing, the product was dried. (The granulation room, in addition to having local exhaust ventilation in the weighing area and a changing room for the employees, was equipped with its own air supply forced into the room through ceiling inlets on one side of the room and removed through floor outlets on the opposite side of the room. When active ingredients were handled, the workers wore an air-supplied vinyl suit. At other times, they wore a surgical mask, gloves and personal protective clothing).

After granulation, the mixture was compressed into tablets in an adjacent room equipped with laminar air-flow ventilation, the tablets were inspected and then stored. Packaging was undertaken on an assembly line with automatic blister-packing capability. The assembly line area was locally exhausted and partially enclosed in plexiglass. Nine operators, one line tender, one line specialist, two mechanics, two quality control inspectors and a supervisor worked on each shift. They wore overalls, head gear, disposable surgical masks and finger cots. The room was air-conditioned. There were 14 office staff.

Symptoms in female employees were first reported within 6-12 months of starting work (six months before the study). The main complaints were bleeding between periods with or without irregularity of menses. The first male employee complaint occurred in April 1975 and six months months after commencing work. He complained of itching and tingling of the nipples, which progressed to frank enlargement of the breast with a milky white discharge from the nipple. He also complained of loss of libido and progressive impotence.

Question 2

a) Discuss the possible etiologies of these complaints.
b) With a feminizing syndrome fairly well established, how would you proceed to verify the diagnosis in the index cases and review the remainder of the workforce?

PART 3

Fifty-five of the 57 employees were available for study (two were off sick with unrelated complaints). A questionnaire covering the points outlined in Part II was administered and each employee was given a short physical examination designed to detect clinical hyperestrogenism. A blood sample was then taken for exogenous estrogen analysis. Two persons refused the examination, and one of these also refused the venipuncture.

Question 3

a) This investigation contains a highly sensitive health review. How might you proceed to achieve a high response rate?
b) How can you validate the clinical findings?
c) How should you proceed to acquire comparison data?
d) How should you analyse the data?

PART 4

The following is a summary of the epidemiological data for all plant employees:

Case No.	Sex	Plant dept.	Case(+) or non-case (-)	Plasma ethynyl estradiol levels (for Normal N)*
1	M	Office	-	N
2	F	"	-	N
3	M	"	-	N
4	F	"	-	N
5	F	"	-	N
6	F	"	-	O
7	F	"	-	No Sample
8	M	"	-	
9	M	"	-	
0	M	"	-	N
11	M	"	-	
12	M	"	-	N
13	M	"	-	
14	M	"	-	N
15	F	Quality assurance	-	
16	F	"	-	
17	M	"	+	
18	F	"	-	
19	M	"	+	N
20	F	"	-	
21	F	"	+	
22	M	Manager	-	N
23	F	Secretary	-	N
24	M	Supervisor	-	N
25	M	Supervisor	-	N
26	M	Supervisor	-	N
27	M	Process technician	+	N
28	M	"	+	N
29	F	"	+	
30	M	Line inspector	-	N
31	M	"	-	
32	M	Mechanic	+	N
33	M	"	-	
34	M	"	-	N
35	M	Line tender	-	
36	M	"	-	N
37	M	Custodian	-	N

38	F	Packing operative	----------OFF SICK----------	
39	F	"	-	N
40	F	"	+	N
41	F	"	+	N
42	F	"	+	
43	F	"	-	N
44	F	"	+	N
45	F	"	-	
46	F	"	+	N
47	F	"	+	N
48	F	"	+	N
49	F	"	-	N
50	F	"	----------OFF SICK----------	
51	F	"	-	
52	F	"	+	N
53	F	"	+	N
54	F	"	-	N
55	F	"	-	N
56	F	"	-	N
57	F	"	+	N

*Elevated levels = 30 pg/ml for women not currently using oral contraceptives, and for all men.

150 pg/ml for women currently using oral contraceptives.

Question 4

a) Calculate the departmental attack rates by sex (the departments were: office, quality assurance, process technician, packing operatives, other production staff).

b) What do these results suggest?

c) Devise a table of elevated plasma ethynyl estradiol levels by department. What does it show? What errors may have led to this unimpressive result?

PART 5

The following tables show the results of comparing menstrual history data of the factory populations (office versus non-office) with the controls.

Table XI shows the results for ungrouped data.

Table XI. Comparison of menstrual history data for past twelve months for 30 female factory employees and 60 matched controls.*

	Factory workers (N=30)		Controls (N=60)	
	MEAN	S.D.	MEAN	S.D.
Age of menarche	12.3	1.1	12.5	1.5
Frequency of menstruation	28.1	0.4	28.8	4.0
Duration of menstruation	4.1	1.1	4.1	1.1
% with intermenstrual bleeding (all categories)	40%	(12)	16.7%	(10)
Category 4 & 5 office workers	0%	(0)	20.0%	(4)
Category 1, 2 & 3 non-office workers	50%	(12)	15.0%	(6)

* Source - Harrington, et al. 1978, Table 2, p. 13.

Table XII shows the results of matched pair analysis (two controls for each factory worker).

Table XII. Comparison of intermenstrual bleeding history in office workers (categories 4 & 5) and plant workers (categories 1, 2 & 3) and controls by matched pair analysis

Intermenstural bleeding	Office workers No. of controls			Non-office workers No. of controls		
	2	1	0	2	1	0
Factory +	0	0	0	0	2	10
Factory -	0	1	4	0	5	6
Estimated Relative Risk (RR)		0			4.26	
95% Confidence Limits				1.6	-	11.3

Question 5

a) Are you impressed with the matching procedure as judged by the comparisons of age at menarche, frequency and duration of menstruation?

b) Does Table XII add more weight to your conclusions from Question 4b?
c) What further data should be included in your assessment of the probable workplace hazard?

PART 6

Industrial hygiene data

The industrial hygienists undertook a walk-through tour of the plant, inspected the process and decided upon their sampling strategy. This included areas sampling, personal (lapel) sampling and wipe samples from work surfaces.

The results of their survey are shown in Table XIII:

Table XIII. Environmental measurements.

	Mestranol ug/m^3	Norethindrone ug/m^3
Area sampling (6-7 hour sampling time)		
Granulation room	1.10	0.94
Compression room	0.73	0.30
Packaging line	2.19-6.47	1.80-11.74
Inspection	0.06	1.33
Packaging room	0.59	N.D.
Personal sampling (6-7 hour sampling time)		
Technician in compression room	N.D.-0.39	11.79-59.56
Line operators	N.D.-8.61	N.D.-43.18
Wipe samples		
Packing room		
- Work bench	0.02	0.12
- Opposite tablet rejection	6.04	31.6
Employees clothes	3.24-5.24	N.D.-3.60
Changing room	13.24	94.8

N.D. = not detectable.

Question 6

a) Do these data support the a priori risk grouping done at the start of the exercise?

b) The ratio (weight for weight) of the two active ingredients in the oral contraceptive was mestranol:norethisterone-1:20. Any comments?

c) What hygiene improvements might be implied to be needed from these results?

PART 7

Implications of epidemiological data for standard setting for estrogens

No occupational hygiene standards exist for estrogen, yet this chemical (and other pharmaceuticals) is biologically more potent than many other chemicals and metals for which standards exist. Although the data from this study are insufficiently accurate to be used alone to set a standard, an approximate figure can be calculated thus:

An estimate for safe levels of estrogen in air

50 ug of ethynyl estradiol (EE_2) per day --> FSH (^{o})
--> ? feminizing effect (^{o})

Assume

(1) The "no effect" dose is 100 times less
(2) Oral dose = inhaled dose
(3) Person doing light work inhale 3-8 m^3 of air in 8 hours.

Then

No effect EE_2 concn. = 0.06 to 0.16 ug/m^3.

Clinical effects would occur at concentrations between 6 and 16 ug/m^3.

	n	Mean	S.D.	Range
Area samples (ug/m^3)	10	1.43	1.91	0-6.47
Personal samples (ug/m^3)	13	1.96	2.46	0-8.61

Question 7

a) What comments have you to make on the validity of the above exercise?
b) What implications would such a standard, if accepted, have on the manufacture and formulation of estrogen containing preparations?
c) Are formal standards based on better evidence then this?

PART 8

Concluding remarks

The investigation studied here shows that with relatively simple epidemiological techniques, a worker-initiated study was capable of demonstrating fairly conclusive evidence of an occupationally induced illness. This association of exposure with effect was rendered easier by the absence of any other serious etiological contender, the single purpose of the workplace - namely to formulate oral contraceptives - , the short life span of the factory, the absence of any appreciable labour turnover and the severity of the health effects - particularly in the males.

Some serious methodological shortcomings are, however, highlighted: the plasma ethynyl estradiol levels were not precisely timed nor were they accurately related to the timing of last ingestion of prescribed oral contraceptive pills. No other measures of overian/testicular function were undertaken for exclusory purposes. Furthermore, in a less obvious outbreak, the clinical outcome measures of gynaecomastia and a past history of intermenstrual bleeding might have proved too crude an index of dysfunction.

Although this study is the first to highlight the occupational hazards of a modern pharmaceutical plant handling potent sex hormones, it is predated by a report of Scarff and Smith in a diethy stilbestrol plant in 1942, and Fitzsimmons in 1944. Even children have been affected by their fathers contaminated clothing. Nevertheless, the present study emphasizes the scrupulous care needed to avoid unwanted worker effects when dealing with potent biologically active agents. This is a generalized problem of the pharmaceutical industry which is largely unreported in the medical literature.

Suggested Reading

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INSTRUCTOR'S NOTES
GYNAECOMASTIA IN ESTROGEN EXPOSED WORKERS

Introduction

In brief, reports of disease in workers led to an investigation of estrogen related health effects in workers manufacturing pharmaceuticals. The primary methodology used in this investigation was a cross-sectional survey for signs and symptoms of exposure and a determination of biological levels of estrogenic steroids. A comparison population served to establish rates for symptoms established in the cross-sectional survey. An industrial hygiene survey was conducted to measure exposure and validate the categorization of exposures used in the epidemiological investigation. This teaching case serves to demonstrate the exceptional value that can derive from observations made by workers. Also, it demonstrates that simple investigational designs may be quite adequate when the cause-effect relationship is quite prominent.

PART 1

Question 1a

Clearly there are a number of steps that could be taken. None is foolproof. Some aspects covered in this study included:

i) An agreement before departure as to who was in overall charge of the investigation.
ii) A clear understanding of the individual responsibilities.
iii) One of the hygienists and one of the epidemiologists spoke fluent Spanish.
iv) Agreement was reached amongst the team members concerning who should deal with the press.
v) An agreed approach to the management and the workforce was established before leaving Atlanta through discussions with the Puerto Rican health authorities and the US-based headquarters of the pharmaceutical company concerned.
vi) A female Puerto Rican gynaecologist was added to the study team to help with the health reviews of employees.

Question 1b

Essential preliminary information:

i) nature and history of workplace, numbers of employees by department and process; and
ii) further details of nature and duration of workers' complaints.

146

PART 2

Question 2a

Causes of gynaecomastia. In this instance it is fairly straightforward as both males and females complained of symptoms associated with estrogen exposure in a factory handling estrogens. Nevertheless, you should direct the class to consider non-occupational causes of gynaecomastia and menstrual disorders.

Gynecomastia is not an uncommon event. The commoner causes are:

- puberty and old age,
- hypogonadism - primary (including Klinefelter's syndrome),
  - secondary,
- obesity
- neoplasms,
- systemic disease, e.g. malnutrition, renal failure, hepatic disorders,
- drugs, e.g. digitalis, phenothiazines, marihuana, cytotoxics,
- and perhaps less well described, asymptomatic normal men (up to 30% in some surveys.

Menstrual disorders are very common. The students should begin, therefore, to contemplate the need for referent populations - perhaps within the workforce and without.

Question 2b

Establishment of cases and non-cases

In a factory of this size, all employees should be reviewed. This entails a detailed history of present complaints, past medical history, status, medication, liver disease, as well as clinical examination, and blood samples for estrogen estimation.

PART 3

Question 3a

Remember this investigation was widely - even sensationally - publicized, and the demand for an inquiry arose from the workers. Nevertheless, several steps were taken to aid what turned out to be virtually complete cooperation from the workers:

i) The management and employee representatives (nonunionized workforce) had the whole investigation outlined to them and an agreed procedure was adopted.

ii) After introductory remarks by the manager and shop floor representative, the chief investigator outlined the plan to the whole workforce at a meeting in the factory with simultaneous translation into Spanish. A question and answer session followed.

iii) The questionnaire was administered by the Puerto Rican gynaecologist and the physical examination was undertaken by the CDC epidemiologists chaperoned by a female plant employee. In the main, the examination was centred on the examination of male breasts, though signs of endocrine disorders and hepatic dysfunction were looked for in both sexes.

Question 3b

Menstural history is notoriously inaccurate. Ideally, diary cards kept prospectively would have been a better plan, but in the circumstances, reliance was placed on past history during employment in the plant and the collection of identical data from referent populations.

An a priori case definition for male and female hyperestrogenism was established to distinguish "case" from "non-case". The short working lifetime of the factory was an advantage here. The definitions were:

Male: An employee who, since working at the factory, had had gynaecomastia (enlarged or swollen breasts or areolar area on history or examination) or decreased libido with increased areolar pigmentation.

Female: An employee who, since working at the factory, has had at least one episode of vaginal bleeding other than at menstruation.

i) the long and detailed questionnaire proved unnecessarily extensive as the workers' initial complaints proved to be the crucial questions

ii) both the CDC epidemiologists discussed the clinical confirmation of gynaecomastia with endocrinologists before leaving Atlanta. In practice, the breast enlargements were gross and in one case was accompanied by demonstrable galactorrhoea and in another the enlargement was unilateral.

Question 3c

The brighter students should be beginning to question whether a risk-group categorization of the workforce is in order, and be demanding some comparison data collection. The without-factory control populations were acquired for female employees (due to the potential bias in collecting menstrual history data) by applying the same menstrual questions to women attending cervical screening and well women clinics in the San Juan-Dorado district. This is not ideal, but age, socioeconomic matching and a comparison of these results with the limited published data showed that it was a reasonable choice of control subjects. In addition, the factory workforce was divided into five a priori risk groups depending on their potential exposure to estrogen dust - see Part 4.

Question 3d

i) Attack rates were calculated for hyperestrogenism.

ii) Calculations for factory groupings versus control populations for intermenstrual bleeding could be done by a simple X^2 technique.

iii) Plasma ethynyl estradiol levels by risk group category were analysed using X^2 with a Yates correction for small numbers.

PART 4

Table XIV. Prevalence of clinical hyperestrogenism in plant employees by job category*.

		Males		Females	
Category	Job	Number of employees at risk	Cases (%)	Number of employees at risk	Cases (%)
1	Processing technicians	2	2 (100)	1	1 (100)
2	Quality assurance	2	2 (100)	5	1 (20)
3	Production operatives	0	0 (0)	18	10 (55.6)
4	Other production staff	12	1 (8.3)	1	0 (0)
5	Office staff	9	0 (0)	5	0 (0)
		25	5 (20)	30	12 (40)

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* Source - Harrington, *et al*. 1978, p. 13 Table 1.

Question 4a

i) It is clear that the process technicians and quality assurance staff are, indeed, more likely to be affected and are certainly those at greatest risk of exposure to the active ingredients. The office workers are rarely in the plant itself.

ii) It is impossible to estimate the significance of the 55% attack rate in female process workers without comparison to comparable populations, though the rate for female office staff is none out of five (see Table XI, p. F 5).

iii) The astute student may note the one male case amongst the "other production" staff. He was the mechanic who changed the filters in the granulation room. He was highly likely to be exposed to pure active ingredient, and therefore, may be considered inappropriately classified on the *a priori* risk groupings.

Question 4b

There is strong evidence of an association between occupation and hyperestrogenism.

Question 4c

Table XV. Plasma ethynyl estradiol (pg/ml) estimations grouped by job category.

Category	Job	Number of employees with elevated levels*	Total population
1	Processing technicians	1	3
2	Quality assurance	6	7
3	Production operatives	3	18
4	Other production staff	3	13
5	Office staff	5	13

For category 1 & 2 versus category 3, 4 & 5, X^2 (with Yates Correction) = 2.99 (p = 0.08)

*Elevated levels = > 30 pg/ml for Women NOT currently using oral contraceptives and for all men

> 150 pg/ml for Women currently using oral contraceptives

However one groups the data, the only comparison which comes even close to statistical significance is the one indicated in Table XV.

Plasma ethynyl estradiol levels vary with time of day, exposure - occupational and therapeutic - length of exposure and time since last exposure. The venipunctures were done at the time of the clinical examination and no regard was taken for the above variations. This was a serious methodological shortcoming, and greater care in timing of samples, knowledge of timing of therapeutic dosage (if appropriate), and time during the work cycle might have given different results.

PART 5

Question 5a

The good student should realize that menstrual history data is notoriously unreliable. Most women (of these ages), when questioned, will say that their periods started about the age of 12 years, last for about four days and occur every four weeks. The closeness of the comparison here probably says more about the comparable inaccuracies of the data than the exactness of matching procedure.

Nevertheless, intermenstrual bleeding is a significant clinical sign. There is little difference in the control population between the reporting rates for office workers and factory process workers. The difference is great, however, within the factory.

Question 5b

The results in Table XI are statistically significant on a X^2 analysis, but the data were matched and should be analysed as matched pairs. The iterative method of Miettinen* is appropriate and can be done using a programmable calculator. The results add considerable weight to the hypothesis that these workers have occupationally related hyperestrogenism.

Question 5c

Industrial hygiene measurements - see Part 6 below.

PART 6

Question 6a

i) To some extent, yes. The area samples and personal samples suggest that in granulation and compression (where the most florid cases occurred) considerable active ingredient dust was generated despite the stringent precautions.
ii) However, the highest levels for mestranol were noted on the packaging line, a considerable amount in the changing room and also on employees' clothes.

Question 6b

The ratios (weight for weight) in the samples were not 1:20. This could be because one product was lost differentially in the sampling or analysis stages, or that the particle size and weight of the ingredients afforded them differing airborne properties - such as settling time.

Question 6c

The plant was, by and large, modern, efficient, and well run. The size of the health problems serves to emphasize the potency of the product (see Part 7 below).

Nevertheless, some improvements were in order and were complied with:

i) increase of exhaust ventilation in tablet inspection areas;
ii) provision of gloves, not finger cots, for the line operatives;
iii) use of more appropriate and more efficient face masks;
iv) the taking of particular care for the protection of the maintenance staff;

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* Miettinen, O.S. Estimation of relative risk from individually matched series. Biometrics, 26: 75-86 (1970).

v) reevaluation of the hazards of quality assurance work;

vi) provision of an airlock between the comparison/granulation area and the shower room; and

vii) stepping up employee education programmes.

PART 7

Question 7a

i) This procedure, as outlined, is clearly inadequate but has some merit. The assumption concerning the biologically active dose of EE_2 is debatable - it might well be lower for some women and the evidence for a relevant dose in men is meager.

ii) The safety margin of 100 is generous but not unusual.

iii) The oral dose is almost certainly not equivalent to the inhaled dose. Inhalation of such materials is likely to lead to more efficient absorption, but the human data to support that statement for these hormones is lacking.

iv) Some authorities would dispute the figure of 3-8 m^3 of air for light work respiration. Even if acceptable, its range is very wide.

v) No account is taken here of mouth breathing versus nasal breathing.

Question 7b

An airborne standard of, say 0.1 ug/m^3 is so low that it would, for all practical purposes, necessitate total enclosure of all processes using the material. The effect of this on current pharmaceutical industrial practice would be extensive and expensive.

Question 7c

Unfortunately, standards are often based on less relevant and reliable evidence than cited here. Many standards are based primarily or solely on animal data and it has been estimated that many current standards are founde on such extrapolations or on analogy with other chemicals for which standard have a firmer human basis.

G

LEAD AND RENAL ABNORMALITIES
A CASE STUDY*

PART 1

It is 1976 and you have just arrived at the US National Institute for Occupational Safety and Health (NIOSH). Your first assignment is to respond to a hazard evaluation request from the United Chemical Workers Local No. 101 regarding workers at Lead Industries Inc., in Smallville, Tennessee. Air measurements have shown excessive exposure to lead dust at this plant which manufactures chemicals containing inorganic lead. The union requests medical evaluation of lead exposed workers, and expresses additional concern about the company practice of chelating workers with elevated blood lead levels.

Question 1

How would you proceed at this point? Who should you call? What additional information should you seek?

PART 2

Preliminary Information

You first call the union representative who requested the hazard evaluation. The shop steward tells you that the plant employs approximately 70 production workers in the lead chemicals area. Since 1925, this company has produced a variety of lead chemicals such as oxides (red lead and litharge), sulfates, and others. He tells you that the US Occupational Safety and Health Administration (OSHA) inspected the plant in 1975 and that levels of lead dust in the air of several departments were above the 1975 OSHA limit of 200 ug/m^3. OSHA cited the plant, but the company was allowed to operate, provided that workers in the high lead areas wore respirators. Some workers continued to have high blood leads. In addition, the union was suspicious that measurements of blood lead by the laboratory used by the company might be falsely low.

Your next call would be to the plant manager who was surprised to receive your call, since he was unaware that the union had submitted a request to NIOSH. He tells you that OSHA has inspected the plant several times, and to his knowledge, all of the minor problems that existed have been corrected. He states that he must consult with corporate management before proceeding. Some hours later, a lawyer from the company calls you and says that the company will cooperate with NIOSH, but may bring legal action against you and the government!

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* By Michael J. Thun & Edward L. Baker, 1983.

You then arrange the date of the first visit to the plant. You also contact the regional OSHA and learn from the industrial hygienist, who inspected the plant, that OSHA may revisit the plant soon. As a matter of courtesy, you also contact the state epidemiologist, and the NIOSH regional representative.

Question 2

a) Given what you know at this point, what are the immediate public health questions to be addressed?

b) By what methods can you do this?

PART 3

The opening conference, attended by management and union representatives, is relatively uneventful. In the plant you notice signs advising against eating or smoking in production areas. Workers in dusty areas are wearing respirators and uniforms which you are told are provided daily by the company and are not worn home. By talking to workers and examining the personnel records, you learn that this is a very stable workforce. There are approximately 60 non-salaried production workers in the lead areas. All are white, male, and have worked from four to thirty years.

In the medical department, you ask to examine the laboratory records of blood lead. Samples are submitted semi-monthly to a contract laboratory. These are identified only by number on the sheets, and in general, range from 40-100 ug/dl (the upper limit used by OSHA in 1976 was 80 ug/dl, the current OSHA upper limit is 50 ug/dl). The plant physician tells you that he examines workers monthly to detect the acute symptoms of lead intoxication and to check for anemia. It is company policy to administer oral EDTA (ethylene diaminetetraacetic acid) to workers with mild symptoms or signs of lead poisoning. Such workers are allowed to continue working during the course which lasts from seven to ten days. Occasionally, severely symptomatic workers have been treated by the plant physician with intravenous EDTA and removed from exposure. Anemic workers receive ferrous sulfate tablets.

Question 3

Because this plant has declared itself unable to meet the OSHA standard for airborne lead through engineering or ventilation controls, it is relying upon respirators (personal protection devices) as the major control measure. What are the limitations of this strategy?

PART 4

Measurements of blood lead

You decide to conduct a cross-sectional survey of current workers. Your initial examination includes 43 (65%) of the 66 workers listed by the company as non-salaried chemical workers. The shop steward tells you that the 23 non-participants have worked at the shop longer, are older, and are reluctant to participate for fear of offending the company. The distribution of blood lead (PbB) measurements on 42 of the 43 participants is as follows:

Table XVI. Distribution of blood lead (PbB) levels.
(N=42, Range = 39-135 ug/dl)

PbB (ug/dl)	Number of participants	Percentage
20-39	1	2.4
40-49	7	16.7
60-79	21	50.0
80+	13	31.0

Question 4

How do you interpret these blood lead levels?

PART 5

Because of the union's concern about the accuracy of blood lead measurements performed by the company's contract laboratory, you decide to "split" nine samples between the company contractor laboratory and a CDC selected regional reference laboratory. The results are:

Table XVII. Comparison of blood lead measurements by the company company contractor compared with those of a regional laboratory.

Sample number	Contractor result (ug/dl)	CDC certified result (ug/dl)
1	63.3	84
2	62.5	79
3	60.8	64
4	64.1	73
5	63.3	75
6	81.0	121
7	56.5	75
8	68.4	75
9	55.0	39
Mean	63.9	76.1

Question 5

a) How would you interpret these results?

b) What additional information would be useful in this interlaboratory comparison?

c) How would you test the statistical significance of the difference between these measurements?

PART 6

Health Effects

Based on the above blood leads, you communicate in an interim report to the union, company, and OSHA that exposures at this plant have been excessive, and that the contract laboratory is underestimating the levels of blood lead.

Included in your cross-sectional medical survey were a number of questions intended to determine the prevalence of lead-related symptoms, and several medical tests to determine organ system impairment.

Question 6

a) Since the effects of lead are well established, and since one can establish the need for more stringent control using exposure data alone, why bother doing medical testing?

b) What are the major health effects of lead? Given these, what medical tests might have been appropriate to include in the cross-sectional study?

You are aware that the Occupational Safety and Health Administration has begun hearings for the proposed lead standard. These hearings have focussed concern upon the chronic effects of lead on the kidney, a subject that has received little recent attention. In children, acute lead poisoning causes the acquired Debre-Detoni-Fanconi syndrome, a complex of disordered functions of aminoaciduria of the renal proximal tubules. In adults, lead nephropathy is characteristically clinically inapparent until it presents with chronic interstitial nephritis, and end-stage, dysfunctional kidneys (Lilis, et al. 1968; Wedeen, et al. 1975; Baker, et al. 1980). Although "saturnine gout", and small scarred kidneys due to lead nephropathy were reputedly common in industrial populations in 19th Century Europe, it is unclear whether lead nephropathy continues to be a problem (Bell & Sorensen, 1969). You decide to look further at this issue.

Two crude measures of renal function (blood urea nitrogen and serum creatinine) were included in the cross-sectional study. At issue is the possibility that chronic, silent loss in renal function may be an underrecognized effect of long-term lead exposure (Goyer & Rhyne, 1973; Lilis, 1981). Your results are:

Diagram of renal function tests in lead workers.

Creatinine (Observed range: 0.8 to 1.4 mg/dl)	
0.	8 8 8
	9 9 9 9 9 9 9 9 9 9 9 9
1.	0 0 0 0 0 0 0 0 0
	1 1 1 1 1 1 1 1
	2 2 2 2 2 2 2
	3 3 3
	4 Upper limit of normal

Blood urea nitrogen (Observed range: 11 to 30 mg/dl)	
1	1
	2
	3 3 3 3 3
	4 4 4
	5 5 5
	6 6 6 6 6
	7 7 7 7
	8 8 8
	9 9 9 9 9
2	0 0 0 Upper limit of normal
	1 1 1
	3 3 3 3
	5
	6
	8
3	0

Question 7

a) What kind of diagram is this?

b) How would you interpret the results?

PART 7

The follow-up medical study

Because of the apparently high prevalence of abnormal blood urea nitrogen (BUN) values noted on the initial screen, you suspect a previously unrecognized epidemic of lead nephropathy. However, your colleagues point out that BUN is a crude marker of reduced renal function. Because BUN is increased both by dietary protein and by dehydration/haemoconcentration, the observed values may not be due to renal disease. In fact, they might be explained by the hot, dry occupational environment and resultant dehydration. Neither does the absence of observed increases in serum creatinine shed light on this question, because the small increases in an individual's serum creatinine that accompany early glomerular disease are obscured by the large variability among healthy individuals.

To complicate matters, the preferred technique for evaluating glomerular dysfunction, measurement of creatinine clearance, is extremely difficult to obtain in a field setting.

Question 8

If you were interested in further assessing the relation between lead exposure and renal dysfunction in these workers, how would you proceed?

Design and results of the actual follow-up study

In the actual hazard evaluation, a second preliminary survey was conducted which identified six additional workers with BUN above 20 mg/dl. Then an extensive clinical examination was conducted on those workers (n=19) who had an elevated BUN on either of the two screening tests, plus two other workers whose blood values had been normal, but who had received EDTA chelation. The examination involved measurement of timed creatinine clearance and of urine osmolality in the office of a local nephrologist following water deprivation. Its purpose was to obtain additional clinical information on those identified as potential cases. The results of the study are shown in Table XVIII.

Question 9

What do these data tell you? What is the prevalence of low creatinine clearance in the leadworkers? With what would you compare these results?

Table XVIII. Results of renal function tests, Missouri lead plant 1976.

Subjects	Age (yr)	Duration of lead exposure (yr)	Blood lead level (ug/dl)	BUN* (mg/dl)	Hyper- tension	Creatinine clearance+ (ml/min/1.73 m^2)	Fasting urine osmolality++ (mosmol/litre)	No.of courses oral EDTA**
1	56	7	154	44	+	85	—	8
2	48	20	66	30	+	142	—	0
3	37	20	35	29	+	82	871	1
4	47	23	71	29	+	72	588	4
5	45	8	87	25		128	1020	2
6	53	23	61	24	+	91	1025	9
7	52	26	61	25	+	115	650	0
8	38	20	123	22		109	608	0
9	60	25	75	26		75	278	0
10	42	21	66	25		96	1180	0
11	47	7	48	23		108	820	0
12	53	29	96	20		89	708	0
13	35	13	56	21		109	965	0
14	62	16	105	20		97	912	1
15	52	25	78	23		73	286	1
16	53	20	92	22		108	912	13
17	51	7	80	21		65	704	4
18	52	31	55	19		43	652	-
19	29	4.5	58	18		112	1114	-

* Arithmetic mean of duplicate determinations in March and May 1976.

** EDTA, Ethylene diaminetetraacetic acid chelation therapy.

+ Lower limit of normal=91 ml/min/1.73 m^2 (Poskanzer, 1983).

++ Lower limit of normal=800 mosm/litre.

In an attempt to use these data epidemiologically, the authors of this case-study attempted to examine the relation between lead exposure and the level of renal dysfunction. Figures 6 and 7 show the scatter diagrams plotting duration of employment versus creatinine clearance (Figure 6) and versus urine osmolality (Figure 7). Beneath each figure are the slope, t and p value of each linear regression.

Question 10

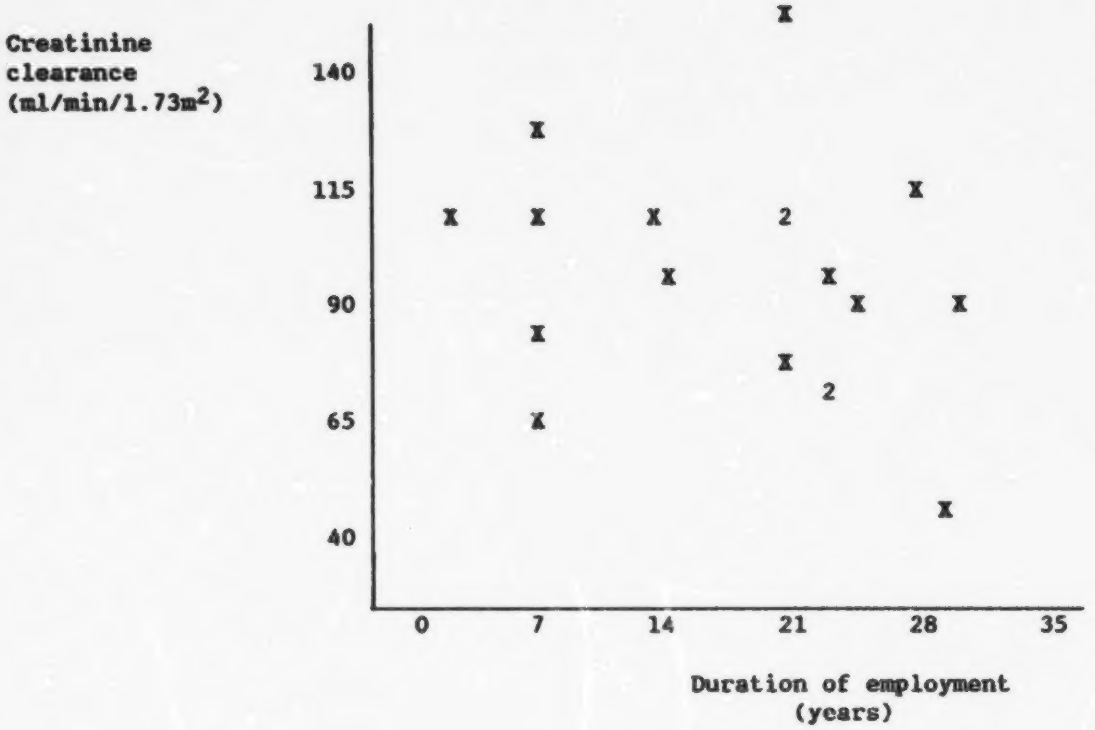
a) How does one assess the " effect" in these linear regression formulae?

b) How do you interpret these results?

c) How do you reconcile the absence of a convincing dose-response pattern with your clinical impression that many of the creatinine clearance values are lower than one would expect in a healthy working population?

Figure 6

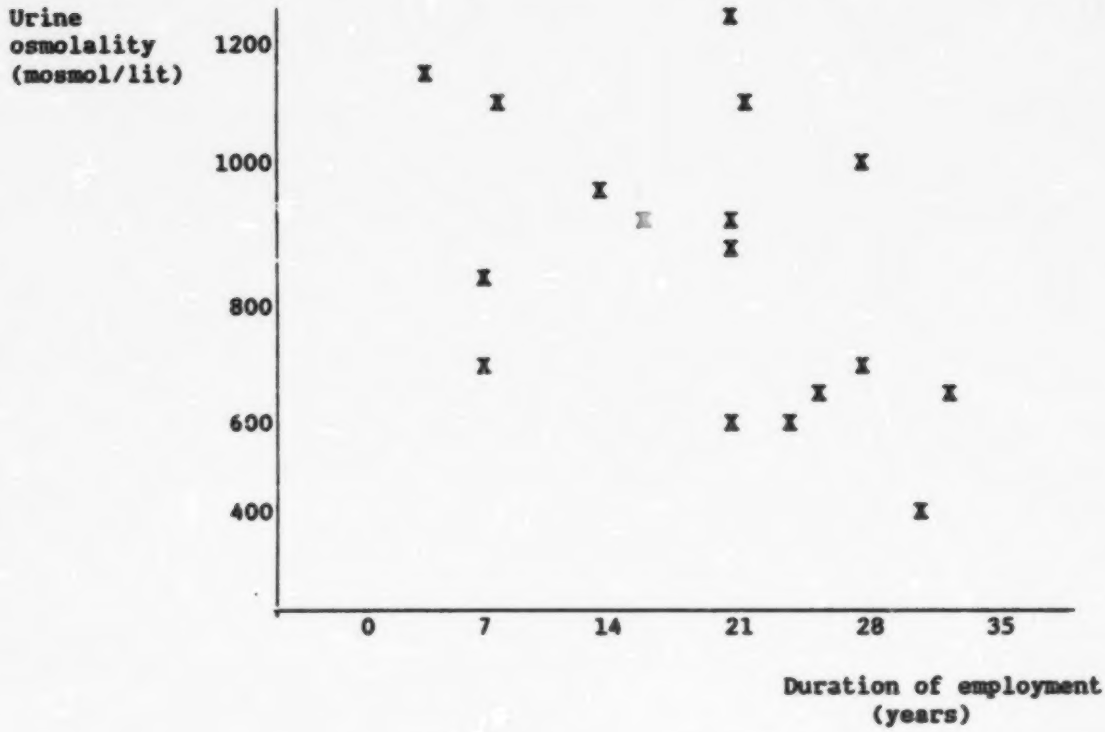
Plot of creatinine clearance versus duration of employment.



Regression of:	B	t	p value
1) Creatinine clearance on duration of employment	-1.02	-2.55	0.1 < p
2) Creatinine clearance on duration and age			
Duration of employment	-0.79	-1.13	0.1 < p
Age	-0.62	-0.94	0.1 < p

Figure 7

Plot of urine osmolality versus duration of employment.



Regression of	B	t	p value
1) Urine osmolality on duration of employment	-15.58	-2.18	$0.01 < p < 0.05$
2) Urine osmolality on duration and age			
Duration of employment	-11.33	-1.43	$0.1 < p$
Age	- 8.60	-1.18	$0.1 < p$

Conclusion

The present hazard evaluation consisted of two distinct phases. The initial survey (actually two surveys) successfully documented that excessive lead exposure was occurring at the plant, and that the existing programme of biological monitoring was inadequate. It also showed what a number of other cross-sectional studies have shown, that the distribution of blood urea nitrogen was shifted upward in the lead workers relative to the general population The follow-up clinical examination was designed to confirm disease status on persons identified as cases by the initial surveys. While it achieved this end, it yielded less epidemiological information than would a study of similar cost and size aimed purely at etiological research. Such a study would have selected subjects solely on the basis of exposure, and would have weighted membership towards the two extremes of exposure, the most highly exposed and the unexposed.

The hazard evaluation is the ultimate in observational epidemiology. Nature, rather than the investigator, has designed the experiment. Within these constraints, the investigator is free to choose the goals of the study, select who should be included, and to obtain information on exposure and disease. This case is intended to illustrate the decision-making process in one such evaluation.

Several important questions remain with respect to occupational lead nephropathy. The most important is whether prolonged exposure to lead, even at levels within the current occupational limit, will damage to the human kidney. The present hazard evaluation could not resolve this question, because the study population was exposed at above the current occupational standard.

INSTRUCTOR'S NOTES
LEAD AND RENAL ABNORMALITIES

Summary

This case-study illustrates a number of steps frequently involved in conducting a hazard evaluation. These include:

1) The need to define the goals of the study at each successive stage.
2) Assessing exposure using biological monitoring data.
3) Evaluating the accuracy of biological monitoring data (using split samples, samples with known concentration, replicates within the same laboratory, etc.).
4) Attempting to use cross-sectional survey data for research, as well as for public health "service" purposes.

The case also provides an opportunity to discuss the health effects of lead, and the advantages of limiting exposure through engineering controls rather than personal protective devices. Two different analytical methods, appropriate for use in analyzing continuous data, are discussed briefly. Part 5 illustrates why a paired Student's t-test is preferable to an unpaired analysis when the data permit. Question 10 illustrates the use of linear regression.

Answer 1

Before visiting the plant, one needs additional information about (1) the nature of the problem, (2) the basis of concern (did it begin with the exposure, or with a cluster of unexplained disease), (3) the type of industrial process, (4) the number of workers in the plant overall and the number affected by this problem (either exposed or ill), and (5) the level of urgency with which a response is needed.

Answer 2

The immediate public health questions to be addressed are: 1) are the exposures to lead excessive? 2) are adverse health effects from lead detectable among current workers? 3) is the company contractor laboratory reliable? Since a great deal is already known about lead and its toxicity, these practical public health "service" questions should be addressed promptly.

The options to consider are 1) to review company records, comparing the industrial hygiene data (air levels) already measured by the plant to existing legal standards, 2) to collect additional industrial hygiene measurements with which to verify company air measurements, 3) a survey of blood lead levels (the biological marker of absorption) to document excessive exposure 4) a cross-sectional medical survey measuring both markers of current exposure (air and blood lead) and measures of the known health effects of lead (erythrocyte protoporphyrin, haematocrit, symptoms of lead colic etc.) or 5) to embark on a sophisticated research study of some unanswered question regarding lead.

Answor 3

Respirators are uncomfortable, they restrict vision and prevent communication, and they require a rigorous programme of continuing education, testing, and maintenance to be effective. Furthermore, relying upon respirators means that only biological monitoring (blood lead levels) can be used to assess control. This has both practical and philosophical drawbacks. The practical limitations are 1) blood lead levels may be reduced by inappropriate medical practices (prophylactic chelation) or inappropriate administrative controls (laying off or rotating workers with high blood leads instead of controlling exposure); 2) measurements done by the company laboratory might be inaccurate.

The philosophical problem is that reliance on blood lead measurement tends to redirect attention away from the issue of exposure and towards the behavioural idiosyncracies of individual workers. Control of lead exposure should be accomplished at the source, through ventilation, enclosure, and where possible, substitution of less toxic substances.

Answer 4

These blood lead measurements clearly indicate excessive absorption of lead. Even in 1976, a blood lead level exceeding 80 ug/dl was considered unacceptable. The OSHA 1978 Lead Standard made the criteria more stringent, requiring medical removal for any worker whose blood lead exceeded 50 ug/dl. Medical removal was to be accompanied by retention of full pay. The blood levels observed here are indisputably too high, in that 31% of the population exceeds 80 ug/dl. (This is a good opportunity to discuss how one determines whether exposure is "excessive" or "acceptable". For example, legal standards may not exist, or they may be out of date because of recent information about toxicity or carcinogenicity. Thus other non-binding scientific recommendations and guidelines should be considered in determining whether an exposure is excessive.)

Answer 5

(a) In all samples except one, the company contractor's measurements were lower than the CDC approved laboratory (on average, 16% lower), suggesting that at least one of the laboratories was wrong.

(b) Without a "gold standard", the company may remain unconvinced about which laboratory is correct. In analyzing lead samples, correctness is usually determined by consensus between laboratories with a proven level of proficiency, rather than by the use of "spiked" known samples. Another test of proficiency could involve the inclusion of replicate samples of the same specimen to assess reproducibility (analytic variability). This setting provides a good opportunity to discuss the reliability (in terms of accuracy and precision) of laboratory measurements.

(c) The class may suggest using either a paired or an unpaired Student's t-test to assess the statistical significance of the differences between the groups. The former has two advantages. First, the variance is smaller, since the measurement of each sample is compared to a second measurement on the same sample. By reducing the influence of interindividual variability, the paired t-test yields a smaller p value (t_8=-2.43, p less than 0.05) than does the unpaired analysis (t_{16}= 1.39, p greater than 0.01). (Note- Because the unpaired t-test requires that the variance of the two samples be equal, log transformation is used to reduce the variance and normalize the data.)

Answer 6

a) Reasons to conduct medical testing include: 1) employee concern about the extent to which the lead has affected individual workers; 2) the possibility that some workers may be symptomatic and may require immediate removal from lead exposure and therapeutic chelation; 3) documentation of the extent of lead-induced morbidity may provide incentive to the company to reduce exposures, and 4) the setting may provide an opportunity to examine some understudied or controversial issue in lead research.

b) The major health effects of lead are haematological, neurological, and renal (Baker, et al. 1979). Lead blocks several enzymes involved in haemoglobin formation (causing anemia, basophilic stippling, and increased erythrocyte protoporphyrin, free erythrocyte porphyrin). Tests that are commonly measured under field settings include haemoglobin, haematocrit, free erythrocyte porphyrin, and less commonly, urinary delta-aminolevulinic acid. Although acute lead poisoning in children causes encephalopathy, chronic overexposure in adults more typically causes a peripheral neuropathy. Sophisticated electrodiagnostic tests, such as nerve conduction velocities, have been used in field settings, but only in special research projects (Baker, et al. 1984).

The renal effects of lead will be the subject of the remainder of this case, and are discussed below.

Answer 7

(a) The so-called "stem-leaf" diagram is a quick, simple way of constructing histograms in the field. It is also an easy way to sort unranked data, and to visualize a distribution (rotate counterclockwise).

(b) Eleven workers (26%) had blood urea nitrogen levels above the laboratory upper limit of normal (20 ug/dl). One would expect only 2.5% in this upper tail, because the upper limit is defined as the 97.5th percentile. Even if these 11 workers were the only workers at the plant with an elevated BUN, these would still comprise 11 of 66 (17%) of the non-salaried workforce. No elevated serum creatinine levels (1.5 mg/dl and above) were seen.

Answer 8

How you proceed depends upon your goal. and on the resources available. If your goal is to confirm the existence of diminished renal function in the workers with elevated BUNs, you might arrange to have only these workers tested with more sophisticated measures of glomerular and tubular function at a local medical facility. This would be expensive and difficult, but would confirm the disease status in the cases.

Alternatively, if your goal is to use a more sensitive and specific marker of renal dysfunction to examine the relation between lead exposure and loss of glomerular filtration rate, you will need to include subjects with the broadest range of exposure levels possible. This will require including unexposed, or less exposed workers in the additional testing. Note- such a study would be a major research project (see Goyer, 1968; Goyer, et al. 1968).

Answer 9

Compared to population "normals", eight of the 19 (42%) tested had a creatinine clearance below the value of 91 ml/min/1.73 m^2 of body surface area (a lower limit of 'normal' defined by Poskanzer (1983). Eight had diminished renal concentrating ability, i.e. urine osmolality of over 800 mosmol/litre after an overnight fast.

The difficulty is the provision of a suitable comparison group, however, the appropriate denominator in calculating prevalence is probably the original group of 42 workers sampled. Thus, the prevalence of low creatinine clearance is 8/42 (19%) rather than 8/19 (42%), since the latter were selected for some evidence of renal dysfunction. Even without a good comparison group, these data suggest a high prevalence of renal abnormalities among the leadworkers. The evidence would be greatly strengthened if an unexposed occupational comparison group of similar age had been tested using the same methods.

Answer 10

a) In linear regression, the measure of effect is the slope. This is given by the regression coefficient, Beta. At issue is whether the slope is positive or negative, and whether it is significantly different from zero.

b) For both variables a weak negative relationship exists, such that with increasing duration of employment, renal function decreases. Duration of employment is a slightly better predictor of both creatinine clearance and urine osmolality than is age alone (a variable closely correlated with duration of employment, r = 0.34). In no case is duration of employment a statistically significant predictor when age is included in the model. (Note- The urine osmolality data contain two outlying data points, which strongly influence the observed regression slope).

c) The best answer is that the tested group represents a selected subset of the plant population. The subjects of this follow-up study were not selected for the purposes of etiological research, but rather, because they had been identified as probable cases by the initial screening. They were chosen for further study on the basis of disease status, rather than exposure. This sampling scheme is useful for confirming the disease status of these cases, but will exclude subjects with low exposure, if lead exposure and renal disease are correlated. In addition, many of the heavily exposed, long-term workers refused to participate in even the initial screening tests. Thus, the combination of practical constraints and the non-research, or service goals of this part of the study may have biased the data towards underestimating the effects of lead.

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H

WASHINGTON SURVEILLANCE PROGRAMME

ARSENIC EXPERIENCE -- A CASE STUDY*

Introduction

PART 1

Many countries collect and tabulate vital statistics including the data derived from death certificates. This example shows how such data may be used. In 1974, an epidemiologist working in the Washington State Health Department in Olympia, Washington, USA sought to use such data for the surveillance of occupational disease (Milham, 1976). In this particular context, the decision was also made to utilize available occupational information on the death certificates. This decision was based on a number of facts:

1. Over 97% of adult male death certificates contained occupational statements.
2. Interviews with next of kin indicated that the death certificate occupational statement was identical to that obtained by interview in 75% of cases and gave a related occupation in 10% of cases (Petersen & Milham, 1974).
3. Case-control studies had shown that the occupational statement on the death certificates were useful (Milham & Hesser, 1967; Milham, 1971).

The coding of occupation is a critical step in this type of analysis. The US Census Bureau occupation code (Government Printing Office, 1960) was used with additions to handle industries and occupations common to the State of Washington or of special interest, i.e., codes were added for many wood products industry jobs, for the aluminum industry, the Boeing Company, the Hanford works (a Department of Energy nuclear facility), etc.

The occupational and industrial statement on a death certificate requires completion of the following information: social security number, usual occupation (give kind of work done during most of the working life, even if retired), kind of business or industry, address, residence within city limits. All the occupations that appear on death certificates can be coded by occupation and industry. The following list is an example of the occupational codes and on the next page an example is given of the occupational coding on death certificates.

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* By Sam Milham, 1983; revised 1985.

Example: Modified Census Bureau Code for Occupation

OPERATIVES continued

CODE NUMBER	OCCUPATION
712	stationary fireman
713	railroad switchmen
714	taxicab drivers and chauffeurs
715	truck and tractor drivers
716	fuel oil truck drivers
717	sawmill truckers
718	lumber and logging truck drivers
719	moving-transfer-storage, workers and truck drivers
720	weavers, textile
721	welders and flame-cutters
722	operatives and kindred workers NEC
724	Forestry Service, Parks, etc.; lookout, game dept. workers, tree farmers
725	sandblasters
726	ordinance plant workers

SERVICE WORKERS except private household

810	attendants, hospital and institutions
811	nursing home, convalescent ctr., hospital managers, owners, etc.
812	attendants, professional and personal service NEC
813	attendants, recreation and amusement(cardroom, poolhall, carnival
814	barbers
815	bartenders
816	cocktail bars, tavern--owners, operators, workers NEC
817	restaurant and cafe owners, operators, workers, managers
818	brewery workers
819	hotel, motel, resort, apartment house, dude ranch; owners, managers, etc.
820	boot blacks or shoe shine operators
821	boarding and lodging house keepers
824	charwomen and cleaners
825	cooks, candy makers, chefs (except private household)
826	dishwashers
827	lumber camp cooks
830	counter and fountain workers
831	elevator operators

Occupational information was coded on the death certificates for all residents of Washington State, age 20 and over, who died between 1950 and 1979. The following table is an example of occupational coding of information on death certificates.

Death certificate Number:	Name:			Job:	Occupational code:
07162	KENDALL	STEPHEN	E	Fiberboard products	500
07167	BUCHANAN	ROBERT	D	Carpenter/Various	411
07171	DRAGER	DONALD	G	Logger/St. Regis Paper Company	970
07172	JOHNSON	STEVEN	C	None	999
07174	SMITH	LAWRENCE		Soldier/U.S. Army	552
07175	VOSSEN	WERNER	F	Carpenter/Carpentry	411
07176	HACKETT	THOMAS	J	Weigh master/American Smelting	435
07179	HARTMAN	FLOYD	W	Carpenter/Construction	441
07180	MARTIN	THOMAS	A	Forklift operator/Lumber company	974
07181	RAFFERTY	JAMES	E	Laborer/Misc.	980
07183	HUBER	JAMES	J	Soldier/U.S. Army	552
07184	MERZ	ANDREW		Longshoreman/Longshoring	965
07185	WEHN	PETER	J	Laborer/Smelter	435
07186	BROCK	JAMES	W	Blacksmith/Self	402
07188	ADAMS	NORMAN	H	Non-commissioned Officer/U.S. Army	552
07193	CRILLY	ROY	F	Laborer	980
07194	ERNST	JACOB	K	Plasterer/Union	505

Question 1

The available data consisted of 310 000 death records. Given this resource, what type of analysis would you use to identify occupations at high risk of specific causes of death in Washington State?

Part 2

The investigator chose to use a proportional mortality analysis. The approach was first tested by noting how well the method could detect previously known associations between exposures and disease. Miners have an increased mortality due to both silicosis and tuberculosis because of silica exposure; asbestos workers have a lung cancer increase, because of asbestos exposure:

PROPORTIONATE MORTALITY RATIOS, WASHINGTON STATE, 1950-1979

			Deaths		
Occupation	Exposure	Disease	Observed	Expected	PMR
Miners	Silica	Tuberculosis	74	14	522**
		Silicosis	42	2	2521**
Asbestos Workers	Asbestos	Lung Cancer	20	5	410**

** $p < 0.01$

Table XIX presents the proportionate mortality ratios for Washington State smelter workers.

Table XIX. Proportionate Mortality Ratios
Washington State, 1950-1979.
Smelter Workers

		Deaths		
Cause of Death	7th ICD	Observed	Expected	PMR
Malignant Neoplasm of Bronchus and Lung	162.1,163	83	50	167**

**$p < 0.01$

Tables XXA and XXB present the methods for computing both proportionate mortality ratios and standardized mortality ratios.

Questions 2

a) How would you interpret this finding? What would be your next step in an investigation of this problem?

b) In general, what is the use of a surveillance analysis of this type?

c) What are the strengths and weakness of a PMR analysis?

Table XX A. Computation of standardized mortality ratios for tuberculosis, all forms, for white miners: USA, 1950.

Standardized mortality ratio

$$= \frac{\text{Tabulated deaths for an occupation-cause-colour group}}{\text{Expected deaths for an occupation-cause-colour group}} \text{ X } 100$$

Age	Estimated population of white miners (Population at risk) (1)	Death rate (per 100 000 population) for tuberculosis, all forms, for all males in this study (2)	Expected deaths from tuberculosis, all forms, for white miners (3) = (1)x(2)	Tabulated or observed deaths from tuberculosis, all forms, for white miners (4)
20-24 years	74 598	12.26	9.14	10
25-29 years	85 077	16.12	13.71	20
30-34 years	80 845	21.54	17.41	22
35-44 years	148 870	33.95	50.55	98
45-54 years	102 649	56.82	58.32	174
55-59 years	42 494	75.23	31.96	112
60-64 years	30 037	82.37	24.74	104
Total:				
25-59 years	...	...	171.95	426
20-64 years	...	...	205.83	540
Standardized mortality ratio	25-59 years= $\frac{426}{172}$ X 100=249		20-64 years= $\frac{540}{206}$ X 100=253	

Table XX B. Computation of proportionate mortality ratios for tuberculosis, all forms, for white miners: USA, 1950.

Proportionage mortality ratio

$$= \frac{\text{Tabulated deaths for an occupation-cause-colour group}}{\text{Expected deaths for an occupation-cause-colour group}} \text{ X } 100$$

Age	Percentage tuberculosis deaths of all deaths all occupations (1)	Deaths from all causes for white miners (2)	Expected deaths from tuberculosis, all forms, for white miners (3) = (1)x(2)	Tabulated deaths from tuberculosis, all forms, for white miners (4)
20-24 years	6.28	292	18.34	10
25-29 years	8.30	357	29.63	20
30-34 years	9.01	341	30.72	22
35-44 years	7.78	1095	85.19	98
45-54 years	5.19	1784	92.59	174
55-59 years	3.68	1554	57.19	112
60-64 years	2.77	2051	56.81	104
Total:				
25-59 years	...	...	295.32	426
20-64 years	...	...	370.47	540
Proportionate mortality ratio	25-59 years= $\frac{426}{295}$ X 100=146		20-64 years= $\frac{540}{370}$ X 100=144	

PART 3

In actual fact the investigators knew that there was only one particular smelter (of copper) in Washington State, where substantial exposure to arsenic occurred. They also learned that a study on the mortality of these workers had been conducted by Pinto and Bennett in 1963 of which an excerpt is given below:

	Deaths			
	Non-arsenic exposure		Arsenic exposure	
Cause of Death	Observed	Expected	Observed	Expected
Cancer of lung	15	7.2	3	1.4

Commenting on these figures above, the authors of the study wrote "This comparison shows that there were a few more deaths in the arsenic exposed respiratory cancer group than were to be expected by calculation, and further study of these cases is continuing. At present, we can say that arsenic trioxide was not one of the possible external factors associated with this problem."

Two other pieces of information are available from this paper:

- In the smelter workers, lung cancer caused 15 deaths (42%) of all 43 cancer deaths, whereas for the State out of 2184 deaths due to all types of cancer, 518 (24%) were due to lung cancer; and

- Those employees not exposed to arsenic had an average urinary excretory value of 0.13 mg As/1 of urine, whereas the exposed employees had an average urinary arsenic of 0.82 mg/1 (Pinto & Bennett, 1963).

Normal urinary arsenic levels have varied from study to study, but a study conducted by the National Cancer Institute (Lee & Fraumeni, 1969) found unexposed people to have levels of arsenic in urine averaging 0.0145 mg/1.

Question 3

Do you agree with Dr. Pinto and Bennett in their assessment of the data?

PART 4

Subsequent to the publication of the Washington State proportional mortality rate (PMR) study, the Tacoma smelter hired an outside consultant to have another look at their worker mortality. A more recent study at the Tacoma smelter showed a clearly increased mortality due to lung cancer and an increase in standardized mortality ratios (SMR) with a time-weighted arsenic exposure index (Pinto, et al. 1978).

Other copper smelter worker populations in Japan, Sweden and the USA also showed a lung cancer increase. These included a study at a smelter at Anaconda, Montana, USA. This is an example from a study by Lee and Fraumeni which was published in 1969.

Observed and expected respiratory cancer deaths and standardized mortality ratios by arsenic exposure index

Exposure Index	Mean Index	No. of men	Respiratory cancer deaths Observed	Expected	SMR
Under 2000	1514	36	1	0.9	111.1
2000-2999	2513	109	4	2.1	190.5
3000-5999	4317	205	11	3.9	282.0*
6000-8999	7473	109	7	2.3	304.3*
9000-11999	10135	38	4	0.7	571.4*
12000 and over	14712	29	5	0.6	833.3*

*p less than 0.05

Question 4

In view of the information presented in Table XX above, how valuable would you consider the PMR approach in Washington State? Note that the finding about the smelter workers was one among many other findings in the surveillance-PMR study.

PART 5

Since copper smelter workers are exposed to sulfur dioxide (SO_2) and other dusts, it is difficult to incriminate arsenic trioxide alone as the responsible carcinogen. In copper smelter environments, SO_2, metallic dusts and fumes, and arsenic trioxide are strongly correlated, that is, high levels of arsenic trioxide are ordinarily found along with high levels of SO_2 and other dusts.

Arsenic trioxide is used as one of the starting chemicals for the production of arsenical insecticides. A 1974 study at Dow Chemical Company among insecticide manufacturers showed a positive lung cancer/arsenic relationship (Ott, et al. 1974), a British study (Hill & Faning, 1948) and one done in Baltimore (Mabuchi, et al. 1979) supported these findings.

Based on the first study of smelter workers in Washington state, described in Part 3, the arsenic 8-hour time weighted average (TWA) worker exposure standard was set at 500 ug/m^3 of air. Note also that animal experiments on arsenic and cancer had not shown any effect so far (recently there has been some experimental evidence). With epidemiology positive and animal experiments inconclusive, the situation was rather parallel to the early days of evaluating the relationship of cigarette smoking and lung cancer. With the accumulation of evidence from the above studies, OSHA lowered the arsenic standard to 10 ug/m^3 of air on an 8-hour TWA.

A sampling of arsenic in air at the Tacoma smelter in 1979 from a publication by Cant and Legendre in 1982, is reproduced as Table XXI.

Question 5

How well does the Tacoma smelter do in meeting the current 10 microgram/m^3 OSHA standard?

Worker protection is attempted through the use of respirators.

Question 6

How could you check to see if the respirators were being used or were doing the job?

Table XXI. Airborne inorganic arsenic (As) levels measured as breathing zone time-weighted averages*

Department	N	As concentration - ug/m^3		
		Range	x	s
Yard, mobile equipment track personnel	11	0.3-80	12.4	23.0
Crushing, sampling and martin mill	28	1.5-110	13.1	20.4
Herreshoff roasters	42	nd-820	169.5	195.4
Reverberatory furnace	20	nd-190	43.6	42.6
Converters	20	15-820	160.4	247.3
Anode furnaces	9	10-60	28.9	20.9
Refinery	15	4-19	9.27	4.67
Refinery by-products	5	5-210	49.0	90.1
Nickel plant	5	4-11	7.4	3.0
Arsenic plant	16	100-1940	548.1	488.5
SO_2/Acid plant	4	5-280	76.3	135.9
Main cottrell	10	nd-6933	1162.7	2170.8
Boiler room/power plant	15	1-160	61.6	51.6
Maintenance	72	0.7-5310	108.3	624.2

N = number of samples; x = mean; s = standard deviation; ug/m^3 = micrograms per cubic metre of air; nd = non-detectable (<0.1 ug/m^3).

Conclusion

The Washington State death record occupational mortality surveillance programme also picked up pancreatic cancer, leukemia/lymphoma, and emphysema in aluminum reduction plant workers and pancreatic cancers and multiple myeloma in workers at the Hanford works nuclear facility. Some of these findings have been substantiated in population based SMR studies.

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*Source - Cant, S.M., & Legendre, L.A., 1982.

INSTRUCTORS' NOTES
WASHINGTON SURVEILLANCE PROGRAMME
ARSENIC EXPERIENCE-A CASE STUDY

Introduction

The objectives of this case are 1) to introduce the proportionate mortality study, 2) to introduce the concept of state-based surveillance systems based on information collected by departments of vital statistics and 3) to relate the role of epidemiology to standard setting.

PART 1

Answer 1

Essentially we have available information on cause of death, occupation and employer, and demographic information on all decedants in the State of Washington. We do not have lists of past employees from any company, nor do we have information on individuals who used to live in the State but migrated out.

Two options for study design are available: we could conduct proportionate mortality ratios (PMR) by occupation and industry looking for diseases in excess or alternately, if we knew which diseases were of interest we could conduct case control studies looking for occupations or employers that appear in excess. The two designs are complimentary.

PART 2

Answer 2

a) Table XX should be gone over carefully with the group. In Table XX A, to calculate the standardized mortality ratios (SMR), the estimated population of white miners (population at risk) (1) is multiplied by the age-specific death rate (from the US Vital Statistics) (2) to give expected deaths (3); expected deaths are then independently summed. Note that the computation of SMR requires characterizing a population at risk and application of death rates.

In Table XX B, the PMR is calculated by multiplying the proportion of tuberculosis deaths of all deaths (1) by the total deaths in white miners (2) to get expected deaths (3). PMR is then calculated like the SMR above. Note that the all causes PMR is 100 (by definition) and that the malignant neoplasms of respiratory and other intrathoraric organs rubrics ICD160-165 (WHO, 1977) have significant PMR increases.

b) This question should raise the issue of the role of surveillance. Surveillance is the collection, analysis, and use of information for the prevention of disease. The use of a surveillance system as devised, (Milham 1976) is to identify high risk occupations and industries in a state in order that preventable occupational diseases can be identified and prevented.

180

c) Weaknesses

1. The PMR is a summary statistic. There may be trends or patterns in the age-specific mortality ratios that are lost in the summary PMR for all ages. An example of age trends among carpenters of Hodgkin's disease may be found in Petersen and Milham (1974).

2. The all causes PMR has to be 100. It therefore says nothing about total force of mortality. The overall mortality hypothetically could be in excess, but the distribution among disease would not be different from the referent population.

3. Since the sum of cause specific PMRs is 100, a cause of death which has a very high or low PMR can cause other PMRs to be artificially high or low.

Strengths

1. Expected deaths are based on identical occupational definitions in all other occupations. By contrast, in SMRs done by the Registrar General of England and Wales and by Guralnick with the US data, the occupational statement on the death certificate "usual occupation" is related to a census count of occupation, which is the current occupation on census day. Therefore, the case definition of occupation derived from the death certificate is not the same as the population as risk definition of occupation derived from the census.

2. In this case, the PMR analysis covers all deaths in the population so there are no problems with control selection.

3. Empirically, PMR results are almost always parallel to results obtained by SMR methods, particularly when there is complete ascertainment of deaths.

4. PMR is fast and easy and will almost always reveal a problem if one exists.

PART 3

Answer 3

Pinto and Bennett in their 1963 study apparently dismissed any association of arsenic and lung cancer, because a similar excess was observed in employees who did not have arsenic exposure. For example the excess in both areas might be attributed to some factor common to both segments of this population such as smoking cigarettes; on the other hand, to have a two-fold excess in lung cancer would require the population to smoke substantially more than the general population who already smokes cigarettes a great deal. Equally possible is missclassification, so that the non-exposed did in fact work with arsenic, or have local environmental exposure in the plant such that the work records did not adequately reflect those environmental exposures within the plant. The students may suggest other explanations. In any case, the original authors seem too definitive in their dismissal of arsenic.

PART 4

Answer 4

Public health workers have learned that there must be a targeting of preventive resources in order to conquer public health problems. An important example from the conquest of smallpox is the use of surveillance to detect cases and then targeting immunization programmes. Similarly with occupational diseases, one must identify specific problems and target these problems for effective intervention. The State-based PMR approach appears to be one possible mechanism for detecting problems.

PART 5

Answer 5

Very badly indeed. Only the nickel plant and the refinery met the standard.

Answer 6

Take a look at the urinary arsenic levels in workers. Workers who do not wear their respirators or who have a bad fit will inhale, absorb and excrete arsenic in urine.

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1

MALE OCCUPATIONAL REPRODUCTIVE DISEASE*

PART 1

A chemical company employing 300 persons produced or formulated ammonia phosphate fertilizers, and various pesticides. The pesticide production was divided into two areas: the Agricultural Chemical Division (ACD) for commercial use and Best Products for household use. For sometime it was rumored among the workers that the male employee in ACD could not father children after working there. Dr M.D. Whorton was invited to evaluate this situation by the union and agreed upon by the company. In July 1977, five men volunteered for investigation. Dr Whorton saw the men, obtained a comprehensive medical history, made a physical examination and laboratory tests and each man provided a fresh semen sample (after abstaining from ejaculation for 72 hours) for examination. Four men were azoospermic (zero sperm count); while one was severly oligospermic (1×10^6 sperm cells /ml of semen); all five had elevated semen follicle-stimulating hormone (FSH) and leutenizing hormone (LH) levels. All other relevant laboratory tests were normal and there were no specific physical findings. All had fathered children prior to working in the ACD. All were evaluated by a urologist, confirming the clinical diagnosis of azoospermia and severe oligospermia

Question 1

What are the known causes of azoospermia and oligospermia?

Question 2

How do you interpret the elevated semen FSH and LH results?

Question 3

How would you further investigate this initial observation of azoospermia and oligospermia among the five volunteers?

PART 2

All the 31 remaining workers in the ACD section were examined on similar lines to the original five workers. The 11 men with vasectomies completed all the examination except semen analysis. Data according to duration of work in the ACD section is shown in Table XXII.

Question 4

Is there a relationship between exposure and sperm count, FSH, LH, testosterone?

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* By M.D. Whorton, 1983.

Table XXII. Data from 35 men exposed to dibromochloropropane

No.	Age	Job	Yrs Occ	Yrs ag.ch	Age last child	B.C.	Want more child	Sperm count x 10	Mot	Morph % Abn	Test	L.H.	FSH	Comments
100	26	Appr.	5.5	0.25	-	Yes	Yes	56	N	11	440	11	2.0	Elevated SGPT GGT
101	30	Oper.	10.5	10	9	No	Yes	0	-	-	560	33	24.3	
102	24	Helpr	2.5	0.08	-	No	Later	156	N	4	544	10	1.6	
103	30	Oper	9.5	9.5	3	0	No	0	-	-	517	11.1	6.0	
104	28	Oper	9.5	3.5	4	Vas	No	NA	NA	NA	322	39.6	38.5	
105	46	S&R	10.5	9.5	22	Vas	No	NA	NA	NA	594	23	6.1	
106	35	Oper	11.0	10	11	Vas	No	NA	NA	NA	462	28.0	7.8	
107	30	Mech	9.5	1.75	4	Vas	No	NA	NA	NA	546	15.5	8.7	
108	39	Oper	11.0	10	11	No	Yes	0	-	-	525	31.4	11.8	
109	37	Oper	11.0	10.5	11	No	Yes	0	-	-	438	23.3	16.5	
110	25	Oper	3.0	3.0	-	No	Later	1	Dn	32	600	24	3.4	
111	59	Mech	24.0	3.0	26	Vas	No	NA	NA	NA	530	24.4	6.4	Has mod. emphysema
112	35	Oper	7.0	5.0	-	Hyst	No	0	-	-	372	22.9	5.9	Out of ag.ch.1972-74
113	30	Helpr	2.25	0.08	3	Yes	No	91	-	-	312	6.0	2.7	
114	21	Helpr	2.5	0.15	1.5	No	Yes	60	N	5	514	18.0	2.1	
115	29	Mech	1.0	1.0	5	No	Yes	11	N	18	857	17	5.2	elev. SGOT/SGGT
117	31	S&R	4.5	4.0	8	No	Yes	0	-	-	408	26	13.4	
118	21	Helpr	2.0	0.15	1	Yes	Yes	99	N	9	453	26	3.5	
119	30	Oper	4.5	3.4	3	Vas	No	NA	NA	NA	396	13	4.9	
120	24	Oper	6.0	3.0	3	No	Yes	1	Dn	N	633	28.8	7.7	elev. SGGT
121	23	Helpr	2.5	0.33	1	Vas	No	NA	NA	NA	640	5.5	1.3	
122	41	Oper	18.0	15.0	15	No	Yes	0	-	-	264	56	15.0	
123	53	Lab	16.0	7.0	21	Meno	No	23	Dn	12	738	9.9	2.4	Lab,1hr/day/AC area
124	43	Suprv	17.0	3.0	2.5	Vas	No	NA	NA	NA	422	6.6	2.5	
125	30	Ware	3.0	0.04	1.5	Yes	Yes	79	N	10	532	6.2	3.8	
126	48	Oper	9.4	6.5	19.0	Vas	No	NA	NA	NA	342	36.1	12.2	
127	28	Lab	3.0	-	1.5	No	Yes	83	N	11	414	4.2	1.9	
129	33	Suprv	9.4	9.3	-	No	Later	0	-	-	403	21.5	8.7	
130	58	Mech	2.0	1.0	28.0	Meno	No	29	-	-	466	19.9	2.9	
132	33	Lab	7.0	0.05	Pregt	NA	Yes	42	-	-	452	31.3	5.4	+ Wife pregnant
133	23	Oper	3.0	0.10	1	Yes	No	45	N	10	558	8.8	1.7	
135	28	Lab	3.0	-	-	No	Later	244	-	-	599	24.5	3.2	
136	35	Suprv	12.8	10.8	13	Yes	No	0	-	-	329	33.6	11.7	
137	38	Oper	10.8	3.6	10	Vas	No	NA	NA	NA	356	15.0	4.0	
138	47	Lab	23.6	-	15	Vas	No	NA	NA	NA	340	6.6	3.0	
139	30	Lab	4.0	-	0.5	Yes	No	69	N	8	275	8.1	1.1	

Key to Table:

(1) Job:

Appr = Maintenance apprentice   Helpr = Chemical helper   Oper = Chemical operator
S&R = Shipping and receiving   Mech = Maintenance mechanic   Lab = Laboratory technician
Suprv= Supervisor   Ware = Warehouse

(2) Yrs Occ = Years employed by Occidental Chemical Company
(3) Yrs ag.ch. = Years worked with agricultural chemicals
(4) B.C. = Use of birth control measures: VAS = vasectomy   Hyst = hysteromyotomy
Meno = menopause   NA = not applicable
(5) Sperm count x 10^6 = millions of cells per ml semen
(6) Mot = Motility: N = normal   Dn = Decreased
(7) Morph = Morphology: %Abn = percentage abnormal cells
(8) Test = Testosterone in ng/dl (normal 300-1000)
(9) L.H. = mIu/ml (normal 15)
(10) F.S.H. = mIu/ml (normal 6)
(11) Comments as noted

PART 3

Table XXIII. Results of laboratory and semen examination among 25 workers according to duration of exposure in the Agricultural Chemical Division

Group	Sperm count x 10^6	Mean duration of exposure (years)	Number	Mean age (years)	Mean sperm count x 10^6/ml	Mean FSH	Mean LH	Mean testosterone
C	>40	0.1	11	26.7	93.0	3.0	15.0	460
B	1<40	1.0	3	45.3	20.0	2.6	14.0	463
A	<1	8.0	11	32.7	0.2	11.3	28.4	459

The difference in sperm count between group A and C was significant at $p<0.001$. The difference in sperm count between group B and C was significant at $p<0.01$

There were only three women workers in ACD, two were secretaries and one had been a production worker for one month.

Question 5

What are your comments on the procedure to examine all workers in ACD; is it necessary?

Question 6

What further evaluation might you have requested on the men?

Question 7

What sperm count level would you use to classify a man as normal or abnormal?

Question 8

What further information may you request from the three female workers?

PART 4

Offers to ten men were made for bilateral testicular biopsies with the use of general anesthesia. They were selected to represent different durations of potential exposure. The following is the summary of the clinical and semen results for the ten men.

Table XXIV Analysis of data of ten men examined with testicular biopsy

		DBCP	Examination of sperm			Testicular	Age of Last
Man	Age	experience (yr)	Count*	Motility	Morphology	spermatogenesis	child (yrs)
1	26	0.25	54	normal	normal	4+	none
2	30	1.75	vas	--	--	3+	4
3	26	3.5 exp 3.0 none	190	normal	normal	3+	wife preg.
4	29	1.0	11	normal	8% normal	2+	5
5	53	lab 1 hr/ day x 7	23	reduced	normal	2+	21
6	28	3.5	vas	--	--	1+	4
7	24	3.0, abs. 10 mos.	1	reduced	normal	1+	3
8	35	2, abs 2, then 3	0	--	--	1+	none
9	37	10.5	0	--	--	0	11
10	39	10.0	0	--	--	0	11

* (X 10^6 cells)

The principal histological findings were related to spermatogenic activity. The ten biopsies naturally tended to separate into three categories. The first was comprised of specimens with normal or slightly decreased sperm formation (patients 1 to 3). In this group, the morphology of germ cells and Sertoli cells revealed no distinct abnormalities by light or electron microscopy. Brief durations of exposure were recorded for two of these three subjects (patients 1 and 2).

A second group consisted of two biopsies taken from individuals with the longest histories of exposure and whose ejaculum was without sperm (patients 9 and 10). In these biopsies, seminiferous tubules were devoid of germ cells when examined by light or electron microscopy. There was no evidence of cellular necrosis, nor were residual bodies found either in the lumina of the seminiferous tubules or within the cytoplasm of the Sertoli cells. These latter cells were no different from normal human control cells. The intercellular junctions were also unchanged, but the number of fat droplets and amount of glycogen seemed moderately increased. Ultrastructurally, the chromatin, nucleoli and the interchromatin substance showed no deviations from normal.

The third group (patients 4 to 8) comprised five biopsies from individuals with reduced sperm counts and histories of dibromochloropropane (DBCP) exposure intermediate in duration between that of the other two groups. These specimens demonstrated moderate to marked diminution of sperm formation. Spermatogenic cells were observed in only a minority of the seminiferous tubules. In the more severely affected individuals (patients 6 to 8), spermatogenic activity was limited to merely a few short segments of these tubules. All stages of spermatogenesis were represented, but spermatocytes predominated. No ultrastructural alterations could be detected in the cytoplasmic organelles and nuclear components of spermatocytes, spermatogonia, or spermatids, and few residual bodies were present. Sertoli cells and their intercellular junctions were well-preserved, appearing similar to those in biopsies of the second group.

Aside from changes in spermatogenic activity, no other consistent features were found within the three groups of testicular biopsies.

Question 9

What do these data tell you?

Question 10

What additional data do you need to determine the etiology of the outbreak?

PART 5

A listing of the amounts of technical material used per quarter from 1968 through June 1977 in the ACD was generated. There were some 200 chemicals used to make 100 products. Heavily used chemicals included: carbaryl, DBCP, diazinon, dinoseb, endosulfan, epichlorohydrin, ethylene dibromide, malathion, maneb, methyl parathion, parathion, toxaphene, and zineb. Other chemicals were not consistently used during the time period or were used infrequently.

DBCP was used extensively throughout the entire period, constituted 20-25% of the entire ACD production during the 10-year period. No production data were available on the amount of DBCP produced prior to mid-1968.

The industrial hygiene studies done in April and July of 1977 showed an eight-hour time-weighted exposure to DBCP in the ACD plant to be less than 0.4 ppm.

Question 11

How would you evaluate the possible hazards from the variety of chemical exposures?

Question 12

What agency registers and regulates use of pesticides?

Question 13

What controls prevail on the manufacture of pesticides in order to ensure safety?

PART 6

A literature search looking for reproductive toxicity revealed that only four of the compounds produced by the ACD had animal evidence for such effects. These were carbaryl, DBCP, epichlorohydrin, and ethylene dibromide. The negative results of many of the other compounds would have been expected, based on the generally known toxic effects.

The following table shows the amount (in kg) of each of the four chemicals formulated by the ACD during the 10-year period.

Since there were no reliable records as to the time any particular employee spent with any particular chemical, all were assumed to have an equal potential of exposure to each.

Kilograms of chemicals used in ACD

Year	DBCP	Carbaryl	Epichlorohydrin	Ethylene dibromide
1969	695789	91628	9772	55007
1970	672077	42592	24716	40676
1971	558748	23681	7586	21610
1972	684669	56581	1207	0
1973	857416	5524	10191	23519
1974	1310823	3939	15118	205651
1975	3407372	5998	8950	18712
1976	10179466	4786	10787	60100
1977	636605	463	7280	36755

The published toxicological report on DBCP of 1961 showed evidence of testicular atrophy at 5 ppm in a subchronic study in rats, guinea pigs and rabbits. The proposed safe limit was 1 ppm. The toxicological literature on carbaryl showed multiple effects on male rodents at intermediate doses. Epichlorohydrin, similar to alpha chlorohydrin, produced epididymal cysts in rats. Ethylene dibromide produced testicular atrophy in rats, only at higher dose than did DBCP.

Question 15

What would you conclude as the most likely etiological agents?

Question 16

How would you prove your assumption?

INSTRUCTOR'S NOTES
MALE OCCUPATIONAL REPRODUCTIVE DISEASE

PART 1

Answer 1

Factors affecting sperm production

a. Anatomical:

varicocele, cryptorchidism, torsion, trauma (pressure necrosis), vasectomy, vasovasotomy, congenital defect.

b. Heat:

fever of 38.5°C for 48 hours within 3-6 months.

c. Infections:

mumps orchitis, veneral disease, prostatitis, epididymitis.

d. Drugs:

alkylating agents, hormones.

e. Toxic agents:

DBCP, lead, marijuana, radiation.

f. Diseases:

endocrine, cirrhosis, and condition producing impotence:

g. The most common cause (excluding vasectomy) is idiopathic.

Answer 2

Follicle-stimulating hormone (FSH) stimulates spermatogenesis. A high FSH with a zero sperm count would indicate a problem in spermatogenesis, not in a blockage to spermatocyte exit. Leutenizing hormone (LH) is frequently elevated in men with high FSH levels.

Answer 3

One needs to know the extent of the problem. Ideally, one would examine all others with similar exposures of jobs in order to find new cases. If the number is too large, a sampling method needs to be developed.

The plan of action in this situation was to examine all workers with common agricultural chemical exposures.

PART 2

Answer 4

Table XXII presents data directly from the researcher's line listing. Discussion should address aggregate analysis of the data. The author's analysis is presented in Part 3. An appropriate alternate analysis might include drawing a scattergram to help to visualize the association of the sperm count to years of Occidental Chemical Company employment and simple regression using years of employment or a multiple regression including the age of the model.

PART 3

Answer 5

If one is able to examine all the workers, one does not have problems with sampling bias. Amazingly, all of the men provided semen samples. Should a control from another part of the plant have been included? This is not necessary for two reasons: (1) there was a major difference in the men tested as shown in Group A and C; and (2) matching and convincing the matched person to provide semen samples might have been difficult, if not almost impossible.

Answer 6

The researchers chose to conduct testicular biopsies, in nine volunteers at the next step.

The class might discuss the need for a pathological diagnosis. Some might argue that the case for cessation of exposure should be made without biopsies; others might argue that knowing the pathological basis for the azoosperm is important clinically in predicting improvements.

Answer 7

The term "oligospermic" has had a changing definition over time. Currently, a man is considered oligospermic if his sperm count is below 20 million sperm cells per millilitre of semen. If a man is oligospermic, he is not sterile or infertile. This is a relative term. The lower the sperm count, the greater the relative infertility. Remember, fertility is a couple effect. As long as a man can produce viable sperm cells, he is theoretically fertile.

Answer 8

Two of the women were secretaries with no exposure; the third had been a production worker for two months. Neither of the secretaries was trying to have children nor was having menstrual irregularities. The production worker had been taking oral contraceptives for several years. Further evaluation of these three was not done based on the above information.

PART 4

Answer 9

The seminiferous tubules were the target for the effects of exposure. It would appear that the primary spermatogonia were the target cells.

Answer 10

What were the exposures? How well can the exposures be quantified? Are there other groups of workers exposed to agricultural chemicals with similar results? What is known about the potential male reproductive tract effects of the exposure agents?

PART 5

Answer 11

A computerized literature search of all the 200 chemicals and 100 products was conducted looking for adverse male reproductive effects. In addition, the company requested similar information from all of its suppliers.

Answer 12

For the USA, the Environmental Protection Agency (EPA). For California, the Department of Food and Agriculture (CDFA). OSHA only regulates the production of pesticides, not uses.

Answer 13

Manufacturers must provide toxicological data to EPA or CDFA in order to register a pesticide. The manufacturer can require EPA to consider all pesticide toxicological information which cannot then be released to the public. Only a small fraction of such information is published in the open scientific literature.

PART 5

Answer 14

Based on the amount produced every quarter, DBCP was the prime choice as an etiological agent. Epichlorohydrin remained a possibility, either independently or as a co-factor, since it was added to DBCP as a stabilizer (1% epichlorohydrin was present in the finished product).

Answer 15

The assumption would require evaluation of other groups of workers exposed to DBCP. The other two products (ethylene dibromide and carbaryl) were not produced consistently. DBCP accounted for 20-25% of all of the volume of products produced in the ACD. Based on the available data, DBCP was the prime suspect; however, this would not be proved solely by the Occidental Chemical Company data.

PART 7

Subsequent developments :

In August 1977, 12 of the first 14 workers examined at Dow Chemical Company's DBCP production facility in Arkansas were found to be azoospermic. Similarly, Shell found workers in two of its facilities (Denver and Mobile, Alabama) to have reduced sperm counts with DBCP exposure.

During 1977 and 1978, eight separate studies were done in Israel, Mexico and the USA on DBCP-exposed workers. Of the total of 508 men examined, 80 (15.7%) were azoospermic, and 112 (22.1%) were oligospermic (sperm counts less than 20 million per ml). These data conclusively showed the adverse effects of DBCP upon exposed male workers.

SUGGESTED READING

Milby T.H., Whorton, M.D. Epidemiological assessment of occupationally related, chemically induced sperm count suppression. Journal of occupational medicine, 22: 77-82 (1980).

A methodological paper.

Whorton, M.D., Krauss, R.M., Marshall, S., Milby, T.H. Infertility in male pesticide workers. Lancet, ii: 1259-1261 (1977).

The data from the initial study.

Whorton, M.D. "Dibromochloropropane", Proceedings of a Workshop for Assessing Reproductive Hazards in the Workplace. DHHS (NIOSH) Publication No. 81-100, Washington DC, 1981.

A review of this episode and problems with such studies.

Whorton, M.D. Male occupational reproductive hazards. Western journal of medicine, 137: 521-524 (1982).

A review of the literature.

Wyrobek, J. et al. An evaluation of human sperm as indicators of chemical induced alterations of spermatogenic functions. A report of the US Environmental Protection Agency Gene-Tox Programme. Motation research, 115: 73-148 (1983).

A comprehensive review of the literature, more than just occupational.

J

MESOTHELIOMA IN RAILROAD WORKERS*

PART 1

NIOSH had been asked to investigate two cases of malignant pleural mesothelioma in retired employees of a major Pennsylvania railroad. You are assigned this investigation. The cases were detected by an astute physician in the first three months of a new practice in this community of 80 000 people. Both men had retired in the preceding five years and had been employed an average of 35 years as a machinist and a boilermaker, respectively. Each denied occupational asbestos exposure, though on close questioning each indicated that magnesium insulation was extensively used in their workplace to insulate steam powered locomotives prior to 1954.

Question 1

Was it reasonable for the local physician to suspect asbestos exposure despite the absence of an apparent history?

Question 2

Given our knowledge of pleural mesothelioma (30-70% attributable to asbestos) is further investigation warranted?

Question 3

How would you begin this investigation?

Question 4

What sources could be utilized to ascertain additional cases in this occupational group?

PART 2

After confirmation of index cases, consultation with referring physician, cases, unions, management, industry, State and Federal officials, you learn the following:

> The facility in question is a railroad shop where locomotives and railway passenger cars are constructed and repaired. From 1902-1954 activities here centered around steam locomotives which required much asbestos in the form of blocks and powder to insulate engine boilers. Asbestos containing materials were also used in the insulation of pipes, railway and refrigeration cars. The bulk of these activities occurred in specific sites including: the locomotive shop, boiler shop, car shop and the engine house. According to the above sources, there does not seem to be any ongoing asbestos exposure. However, you find an article describing the history of the railroad industry which documents a substantial number of railroad workers were exposed to asbestos through 1950.

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* By M. Sepulveda, 1983; edited July 1985.

The greatest source of past exposure was in the locomotive shop, where 1800 workers representing all crafts, were employed and involved the application and removal of asbestos boiler insulation. These activities were performed by labourers, who with tenure might advance to apprenticeship in one of many skilled crafts, e.g. boilermaker, machinist, pipefitter, carman, firemen, oiler, etc. In the period of interest (1902-1950) 2500 workers per year were employed at this facility. The activities at this site were typical of the process in the industry in general which averaged 250 000 workers per year in the interval of interest.

Personnel and medical records have been denied you and only one of the six craft unions has cooperated with you at the local level. Undaunted, nonetheless, you have managed to recruit interest at the US Department of Labor, the epidemiology branch of the State Health Department and the research division of the Federal Railroad Retirement Board. The first could supply employment data, the second death certificates and the third could identify all workers in the industry by occupation qualifying for benefits under the system, i.e. 10 years of service, and could provide occupational, demographic and vital status data.

In the interim you have established a hospital-based search at the three hospitals in the county for mesotheliomas diagnosed in the last five years. This has resulted in the identification of three other cases in former workers at this facility, yielding a total of five confirmed cases in railroad shop workers. The total number of malignant mesothelioma cases diagnosed in this city since 1975 was 13 as determined by your search.

Question 5

Given that there is clearly an excess of mesothelioma in this community, and that exposure is no longer occurring, what further study would you propose to address the other goals stated in Part 1?

Question 6

Suppose that you decide to determine the prevalence of pulmonary disease among living current and former workers:

a) What criteria would you use to select your study group?
b) Would you include a control group?
If yes, who?

If not, why not?

c) What advantage, if any, might there be to examining a population of asbestos-exposed workers, 30 years after exposure terminated?
d) What type of a morbidity study would this be?

PART 3

In the actual study, all workers (current and former) with a minimum of two years tenure at the railroad shop before 1950 and still residing in the community were invited to participate. The focus of the study was on nonmalignant pulmonary disease related to asbestos exposure (pleural abnormalities and interstitual pulmonary fibrosis). Both posteroanterior (PA) and 45 degree oblique radiographs of the chest were obtained. In addition, occupational respiratory symptom and smoking histories were elicited from each participant.

A population of 266 current and former workers participated in the study. Seventy-five percent were over the age of 60 years, and 80% had fewer than ten years of railroad related asbestos exposure. Roentgenographic evidence of asbestosis (diffuse interstitial pulmonary fibrosis) was found in only five workers (2%), whereas 52 (20%) had one or more pleural abnormalities (Table XXV).

Table XXV. Roentgenographic abnormalities among 266 railroad shop workers by occupation [a]

Occupation	Number	Small opacities[b] only	Pleural abnormality[c] ± small opacities
Boilermakers	27	1 (4%)	9 (33%)
Machinists	92	2 (2%)	28 (30%)
Carmen	30	1 (3%)	1 (3%)
Sheetmetal workers	24	0 (0%)	2 (8%)
Labourers	24	1 (4%)	2 (8%)
Electricians	23	0 (0%)	3 (13%)
All other occupations	46	0 (0%)	7 (15%)
Totals	266	5 (2%)	52 (20%)

Source: Sepulveda & Merchant, 1983.

a Main railroad shop occupation prior to 1950.

b Small opacity profusion 1/0 or greater (ILO 1980) by at least two of three "B" readers.

c Pleural thickening and/or calcification noted by at least two of three "B" readers.

Questions 7

How do you interpret these data?

Question 8

a) Considering that the number of exposed workers was about 2500 at each of the years of interest, what do you think of having a sample of 266 workers only ?

b) Do you think this sample is representative of all exposed railroad shop workers ? If not, why ?

INSTRUCTOR'S NOTES
MESOTHELIOMA IN RAILROAD WORKERS

Principles and methods illustrated by this study

1. The evaluation of a cluster.

2. Identification of the objective of the study.

3. Choice of study methodology.

4. Use of a cross-sectional prevalence survey in identifying a high risk group.

PART 1

Answer 1

a) It was reasonable to suspect asbestos, since asbestos exposure is frequently unrecognized, and since it is well known that asbestos was used in steam engines as insulation. At this point we cannot tell whether a clearcut excess of mesothelioma exists. Mesothelioma has an estimated incidence rate of about 1/100 000 population/year. Hence the diagnosis of two cases with the same occupational history in three months may well represent an excess, particularly if there are other unrecognized cases in the community.

b) Asbestos exposure is the major risk factor for malignant mesothelioma; with positive histories obtainable in 30% to 70% of cases (NIOSH, 1980). Students could try to list other possible risk factors.

Answer 2

Clearly there is no need to prove once again the association between asbestos exposure and mesothelioma, lung cancer, and non-malignant respiratory disease. However, there are several reasons for further study: 1) There may be ongoing exposure of current workers. 2) Railroad workers have not been previously described as a population at risk of asbestos-related disease. If excessive exposure is, or was occurring, it would be useful to alert the exposed workers, and the medical community so that appropriate actions could be taken. 3) Appropriate action might consist of controlling further exposure, advising the workers already exposed to stop smoking, and making the disease compensatable under workers compensation systems to relieve individuals of financial burdens.

Answer 3

Index cases need to be reviewed and confirmed; this is of particular importance for diseases such as malignant mesothelioma where the diagnosis can be quite difficult. The union and the company should be contacted to confirm whether or not asbestos exposure occurred and whether it is still occurring in the railroad yards.

Answer 4

It is most efficient to begin with any records that the company and union may keep: pension files, death benefit files, insurance records, disability, compensation etc. Sometime it is possible to learn of additional cases from local hospitals, tumour registries, etc. The record systems available vary greatly between companies and by geographical region, and must be explored in any given setting.

PART 2

Answer 5

Since there is no ongoing exposure, there is clearly no need for an industrial hygiene survey. A geographical-based case control study could be conducted, although with only five cases of mesothelioma, the sample size would be extremely small. A cohort study may show an excess for non-malignant respiratory disease and lung cancer. Unfortunately, such a study would not provide conclusive evidence that the problem was due to asbestos rather than smoking. Furthermore, an excess of malignant mesothelioma may not be detectable in a cohort mortality study, since this disease is not coded as a single disease outcome. In this circumstance, the most useful study may be a cross-sectional survey of the prevalence of radiological pulmonary abnormalities among current and former workers

Answer 6

a) The population to be examined should include both current and former workers employed before the 1950's (the period during which asbestos exposure occurred). Because it is difficult to find former workers who left the job after a brief tenure, some minimum employment criteria would seem desirable. Workers should also be included who have had a range of exposure (high-medium-low), in order to compare subgroups.

b) Considerations to be weighed in deciding on a comparison or control population include:

   i) available data on the prevalence of abnormalities one would expect to detect in the general population or in other asbestos exposed groups;

   ii) the likelihood of non-asbestos-related etiologies for abnormalities observed;

   iii) availability of suitable comparison groups with regard to desired age, sex distribution, etc.;

   iv) the cost of comparison groups, e.g. cost to recruit and examine, cost of follow-up and definitive diagnosis in those with abnormal tests and the risk from testing procedures (x-rays and radiation).

c) A cross-sectional study (Monson, 1980) of a population with 30 years since last exposure has more disadvantages than advantages. The worst problem is that workers who developed lung cancer or non-malignant lung disease may well have died or have left the area. On the other hand, the prevalence of some pleural abnormalities continues to increase in the years following asbestos exposure. Even though the problem is likely to be underestimated, detecting workers with residual pulmonary abnormalities would document that substantial asbestos exposure had occurred. One can then propose the interventions previously discussed.

d) A cross-sectional study of respiratory morbidity in survivors.

PART 3

Answer 7

Even without a comparison group, there is a much higher prevalence of pleural abnormalities in this population than one would expect. (It would be useful to compare the prevalence of pleural abnormalities here with that in the general population, as measured by the Health Examination Survey). It also appears possible that the prevalence is higher among boilermakers and machinists than among other occupations, but since we had no prior information that the exposure of these two occupational groups was higher than that of other occupations, we do not know how to interpret this information.

Answer 8

This is a very small sample of the total population at risk. It cannot be representative, because it represents a survivor population. Many of those exposed before 1950 have died, some of them from asbestos related disease. Others have moved away, and there are no data on the reasons why some have quit or whether they were different from the survivors.

The public health impact of asbestos exposure in this past industry has been and continues to be enormous, given the number of persons employed in the decades before 1950 (Becklake, 1976). For survivors, the confirmation of this exposure by the radiographic findings has pronounced implications for their future health. While pleural abnormalities *per se* have not been shown to have adverse health effects, they are markers of asbestos exposure and the latter places these workers at risk for asbestos-related malignancies.

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K

HYPERSENSITIVITY PNEUMONITIS IN AN OFFICE BUILDING
(A new form of occupational lung disease)*

PART 1

The outbreak

You are called on a Tuesday afternoon, after everyone else has gone home, about an outbreak of disease in an office building. A section head in a federal agency noticed that several of his employees became ill on Monday afternoon in September, several more on Monday night (as he found out on Tuesday), and three of twenty-four did not come to work. He called several colleagues who noted similar occurrences. The State Health Department was called, but since this was thought to be a work-related outbreak, the section head was referred to NIOSH. People had complained of muscle aches, chest-tightness, and fever. He now wishes to know whether he should let people work in the building the next day.

At an opening conference with the agency head, the safety officer, the building manager, the office physician and the union representative, you find that 27 persons went to see the local physician because of illness developing the day before. Nothing was changed in carpet shampoos, detergents, air fresheners, or painting in the building. The air conditioner was turned off over the weekend because cool weather had been expected. When the temperature reached 27°C on Monday morning, the air conditioner was turned on again. There was a computer room with a separate air-handling system that controlled relative humidity much more strictly. There was an old furnace with a flaking asbestos lining. The air intake filter was currently blocked by refuse in the alley.

The building was built in the 1930s and was vacated in the early 1970s. It was reoccupied only four months before the present episode. The building manager explains that the building was flooded while unoccupied. The ventilation system had not been remodelled since 1939. It was a spray water cooler ("air washer"): water droplets were sprayed from nozzles; they vaporized, and cooled the air. Water aerosols (the noncondensed water) were trapped on baffle plates, collected in a sump, and recirculated. The air was ducted through the building driven by two fans. Return air ducts collected the air from the offices and led into a common plenum. During the summer months the fresh air intake has been less than 5%. The air-intake was next to the air handler (in the basement) adjacent to an alley. To the manager's knowledge no processes were changed in the building.

On the walk-through of the building the atmosphere was very humid. The floor of the fan room was covered with backed-up sewage with a somewhat foul smell. The building is an "open-space" office building. There are 40 windows per floor, of which many are open. There is a row of desks in the periphery, then a corridor, and a central part of each floor.

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* By Michael Hodgson & Philip R. Morey, 1983.

Question 1

Given this setting, what working hypotheses would possibly explain this outbreak of reported disease?

Question 2

What information could be collected by questionnaire, environmental evaluation, physical examination, or laboratory testing, which would allow us to test (differentiate between) some of these hypotheses?

PART 2

Questionnaires and symptoms

Out of a total 324 persons in the building, 216 persons complained of at least one symptom (Table XXVI). The number of persons with at least one symptom is listed in Table XXVII. Of the 216 persons with symptoms, 152 were female, 64 were male.

Table XXVI Numbers of persons with complaints on each floor

Floor	Persons with at least one symptom(%)	Total persons on each floor	No. of open windows on each floor
1	15(54)	28	23
2	36(68)	53	13
3	38(68)	56	18
4	41(65)	63	20
5	21(55)	38	24
6	39(76)	51	13
7	26(74)	35	16
Total	216(66.7%)	324	

Table XXVII Symptom prevalence

Symptom	Number with symptom	% of total (basis 216)
Headache	125	57.9%
Muscle ache	146	67.6%
Fever measured	20	9.3%
Fever unmeasured	71	32.9%
Chills	97	44.9%
Nausea	63	29.2%
Wheezing	62	28.7%
Chest tightness or shortness of breath	58	26.9%
Cough	28	13.0%

The questionnaire also revealed that there were 105 persons with three or more symptoms of whom 60 were females and 45 were males. The base population is unknown and so is their sex distribution.

In order to assess the role of ventilation in this outbreak the following studies were made:

a) Relation of illness to location (central versus peripheral):

	Total	Ill	Non-ill	Attack rate (%)
Centre	159	42	117	26.4
Periphery	169	63	102	37.3
		105	219	

b) Illness among persons in the computer room versus central air supply:

	Total	Ill	Non-ill	Attack rate (%)
Computer	8	0	8	0
Central air supply	324	105	211	32.4
		105	219	

c) Of persons sitting in the periphery - Ill versus non-ill by open or closed windows:

Windows	Total	Ill	Non-ill	Attack rate
Closed	90	71	19	78.9
Open	75	31	44	41.3
Total		102	63	

d) Distribution of employees by sex (as potential for confounding):

	Male	Female		Total	% male
Centre	77	90	=	167	46.1
Periphery	140	19	=	159	88.0
Total	217	109	=	326	66.6

Question 3

a) What conclusions can you draw from this data?

b) Do these data influence your interpretation of what is going on?

c) Do you need any further observations or analysis of the above data?

PART 3

Industrial hygiene and microbiological environmental evaluation

Air samples were collected on filter media. Bulk samples of dust from the air supply and air return ducts and a sample of the sump water were collected for culturing and identifying fungi, thermotolerant bacteria, and amoebae.

The relative humidity on several occasions during operation of the HVAC (Heating, ventilating, and air conditioning) system was in the range of 65% to 75%; when the HVAC system was turned off relative humidity was 45% to 55%. Airborne levels of microorganisms were approximately 800 to 1200 colony-forming units/m^3. Formaldehyde and hydrocarbon levels by short-term detector tubes were several orders of magnitude below the threshold limit values (TLV), while respirable dust levels were between 25 and 50 ug/ml. Sampling for fibres showed 0.5 to 1 fibre/m^3.

Question 4

How can we assess whether these conditions are acceptable?

Question 5

What factors influence airborne microorganisms and are there threshold limit values for airborne microorganisms.

Question 6

What other gases and particulates could you sample for?

PART 4

Etiology

To determine the etiology of this outbreak you try to obtain precipitins in cases and controls (Burrell & Rylander, 1981). You are told that the results of precipitins and cultures from the building will not be available for two to three months. After discussion with the Center for Infectious Diseases, it is decided to clean the air-conditioning system with a quarternary ammonia compound, steam clean the room housing the air-handler, and exchange the old baffle plates. Two weeks later a similar outbreak occurs. Because of legal implications the building owners decide to evacuate their tenants and to restructure the building. It is converted into a condominium.

Table XXVIII Number of people with precipitating antibodies against specific antigens grown from Union Building isolates

Antigen	Union Building Ills N=27	Union Building Controls N=28	NonUnion Building Controls N=28
Aspergillus flavus	3	1	1
Aspergillus versicolor	0	1	0
Aspergillus sp. (beige)	1	1	3
Aspergillus fumigatus	0	0	0
Aspergillus niger	1	0	0
Cephalosporium sp.	3	0	3
Cladosporium sp.	1	0	0
Crytococcus sp.	0	0	0
Dematiaceous sp. No. 1	5	0	2
Dematiaceous sp. No. 2	10	6	6
Epicoccum nigrum	7	2	4
Fusarium sp.	7	1	2
Harposporium sp.	2	1	0
Oidiodendrum sp.	3	1	0
Penicillium sp. No. 1	0	2	0
Penicillium sp. No. 2 (tan)	4	6	4
Penicillium sp. No. 3 (yellow)	0	1	1
Phoma sp.	0	0	0
Pithomyces sp.	11	7	4
Rhodotorula sp.	5	3	0
Small brown colonies	5	3	2
Stachyboteys sp.	14	11	6
Trichoderma sp.	1	2	0
Verticillium sp.	2	1	1
Mucos sp.	0	1	0

Question 7

How would you have selected cases and controls?

Question 8

How would you interpret this serological data?

209

INSTRUCTOR'S NOTES*
HYPERSENSITIVITY PNEUMONITIS IN AN OFFICE BUILDING

This exercise has two purposes:

1. To introduce the subject of hypersensitivity pneumonitis (Arnow, et al. 1978) as an emerging occupational problem in what may apparently be a "nonhazardous" setting, and
2. to introduce the basic methodology of investigation of building-associated diseases.

As users of this chapter may not be familiar with either aspect, a list of references has been compiled. This may be of value in further reading. Instructors may wish to read the references before using this chapter in their courses.

From the state of knowledge in 1983, noninfectious building-associated epidemics can be of three categories:

a) Problems can occur through exposure to agents disseminated into a building through the ventilation system. Examples are carbon-monoxide intoxication from an air intake on street level (rush-hour exhaust) or garages, fibreglass from release of glass fibres in ventilation ducts, and rug shampoos that have been associated with respiratory and mucous membrane irritation, and organophosphate-pesticide entrainment.

b) "Stuffy" buildings is a term for the"tight-building syndrome" associated with odors or irritants. Several factors are thought to play a role in its etiology; decreased air filtration rates in energy efficient modern buildings; decreased intake of outdoor air because of energy conservation; increased levels of hydrocarbons and formaldehyde; off-gassing of formaldehyde and other substances from office furniture; and regular office contaminants (particulates and ammonia from copiers, etc). Symptoms include eye and mucous membrane irritation, nasal stuffiness, and fatigue.

c) "Moldy" buildings may be associated with acute, subacute, or chronic infiltrative lung disease (Parkes, 1982). Acute disease has been seen with a high attack rate of allergy four to six hours after exposure, and associated primarily with water sumps (such as home humidifiers and recirculating sumps in "air-washers", a kind of cooling system) (Edwards & Cockroft, 1981). Subacute disease has been seen with lower attack rates, recurrent symptoms with periodicity throughout the work-week (peak occurrence of symptoms has been seen on both Mondays and Fridays), and symptoms such as diarrhoea and arthralgias. The chronic form occurs with an insidious onset, low attack rates, and, as the above two, constitutional (fever, chills, myalgias, headaches, nausea) and respiratory (cough, chest-tightness, and wheezing) symptoms. Subacute and

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John Simon and Tom Waters were co-investigators on the outbreak after which this case study was designed.

chronic disease may be difficult to diagnose and even to associate with an occupational site because of the low attack-rates, the lack of obvious temporal relation to working, and the lack of specificity of laboratory investigations, such as white cell counts and spirometry. Although humidifier fever and hypersensitivity pneumonitis present with the same symptoms, some authors have atempted to distinguish between them. Pickering (1982) lists three distinguishing characteristics: humidifier fever is associated with normal chest x-rays, with higher attack rates, and with a lack of long-term effects. Some authors attribute the differences more to the setting in which disease is detected than the diseases themselves. Humidifer ferver may be detected earlier in groups of office workers than hypersensitivity pneumonitis in more industrial settings, as office workers may complain as a group. Their disease may then not progress enough to present with abnormal chest x-rays. Chronic sequellae and abnormal chesst x-rays are well described in case reports of humidifier fever. For these reasons epidemiology becomes more important.

Exposure to organisms (such as fungi) from outside the building and dissemination through a ventilation system could lead to a similar epidemic pattern.

All of the above considerations must be differentiated from "hysterical" outbreaks by symptomalotogy and epidemic curve characteristics.

Several factors play a role in respect to buildings (Kreiss, 1984) and their construction:

a) Age of the building and dates of remodeling; outdoor air infiltration rates; age of the ventilation system:
b) Structure of the ventilation system (Hughes, 1986): cooling tower; closed system cooling coils or spray washer; humidification possibilities; location of outdoor air-intake; relative humidity of the air in the workplace; contamination of the ventilation system with pools of water under the cooling banks or fans and water leakage into the HVAC (Heating, Ventilation, Air Conditioner) system:
c) Process-changes within the building: exposure to new rug shampoos; machine exhaust; air fresheners; paints; unusual weather occurrences.

PART 1

Answer 1

The working hypotheses are:

a) That the agent is airborne via the building ventilation;
b) That the outbreak is communicable between employees; and
c) That the epidemic is psychogenic in origin.

Answer 2

Hypothesis (1a) might be supported if:

a) Attack-rates differed in portions of the building supplied by different ventilation systems, i.e. on different floors;
b) If attack rates were lower among persons sitting next to open windows, with an outside source of air;
c) If serum precipitating antibodies could be detected among persons in portions of the building supplied by the suspect ventilation system, but not in sections supplied by different ventilation; or

d) If a pathogenic agent could be isolated from the ventilation system in that part of the building with reported health problems, but not from non-affected areas.

Hypothesis (1b) would be supported if secondary cases were occurring among family members or nonoccupational contacts who did not use the building.

The 'mass psychogenic' or 'nonorganic' hypothesis is often invoked when no other explanation is available. In mass psychogenic outbreaks there are often trigger events that precipitate group concern, often of a wide variety of extreme subjective complaints without objective accompaniment. The symptoms are usually non-specific (headaches, dizziness, nausea) or similar to those associated with hyperventilation. Although usually sudden in onset and often severe, they may occur after leaving the workplace and persist inappropriately long. The presence of "powerful" social figures who become ill first, transmission by "sight or sound", and an elevated attack rate among women are often seen. In this case, confirmation of fever and of the consistency of reported symptoms, including muscle aches and chest tightness, mitigate against this hypothesis. As women may complain of symptoms at lower levels of exposure than men, external comparisons are necessary. This last characteristic does remain to be validated.

PART 2

Answer 3

These data show that prevalence is 41% higher at the periphery than at the centre, which mitigates against a ventilation conducted agent. However, the data showing the deficit in the computer area suggests an airborne problem. The data, demonstrating a higher attack rate in the periphery with windows closed as compared to open, also indicates an airborne problem. The data on sex differential in the periphery may support, in some students minds that the outbreak is not mass psychogenic, but these students would have to have prejudged women to be at higher risk of mass psychogenic illness. This may represent more stereotype than rigorous observation.

PART 3

Answer 4

Twenty and five cubic feet per minute per person, respectively, are recommended by the American Society of Heating, Refrigerating, and Air-Conditioning Engineers, Inc. in standard 62-81 (Ventilation for Acceptable Indoor Air Quality) in areas with smoking and without smoking (McNall, 1981).

Answer 5

Moisture content of air and temperature interact; lower air temperature allows less water content for the same relative humidity, or scientifically, as the dry bulb temperature of air is lowered to the wet bulk temperature the relative humidity increases. This occurs in air-washers and at the chiller deck of closed system air-conditioners. A high relative humidity in the presence of condensed water in air-handling units promotes the growth of microorganisms. It is not clear what makes outbreaks of hypersensitivity pneumonitis (HP) occur. The explanations include sensitization to organisms (Schatz, et al. 1979), and exposure to high levels of organisms without sensitization. Sensitization of individuals has not been adequately explained. It is clear that thermophilic microorganisms are very common (only 50% of households without HP contained thermophiles whereas 75% of households with HP contained them in one study).

Answer 6

Problems in buildings are commonly caused by carbon-monoxide, formaldehyde, off-gassing by plastics, ozone, and emissions and vapour from copy machines. Outbreaks have been ascribed to glass fibre released from fibre-lined ventilation ducts and to rug shampoos.

PART 4

Answer 7

Selection of controls: in this case controls were matched for sex, race, and age within five years. The age-matching was chosen because as persons grow older they may be exposed to more organisms in their environment.

Answer 8

Calculating the probability of the distribution of precipitins involves "exploratory statistics". Although there is obviously a hypothesis being tested, the number of hypotheses which are being tested makes acceptance of a falsely positive result more likely. To document safety of the building for reoccupancy the etiology must be known as otherwise it is impossible to show eradication of the disease. Often buildings have been reoccupied without documentation: some of these building have had recurrence of disease.

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CANCER MORTALITY IN A DIE CASTING AND ELECTROPLATING PLANT*

PART 1

On 1 March 1980 one of the vice-presidents of the United Automobile Workers received the following letter from a UAW local union president:

> Dear Brother ....,
>
> Enclosed you will find the results of a recently conducted study involving the Mortality Rate of members of our Local Union, between January 1, 1974 and December 31, 1978.
>
> As the evidence indicates, in this five-year study, our members have within their midst a serious health problem. In view of the magnitude of the situation, I would recommend that appropriate authorities be notified of the results of this study ...."

The accompanying report stated that "It was in 1977 I first became suspicious of the mortality rate among my fellow plant workers. A higher than normal cancer rate seemed to be claiming many co-workers at a relatively young age...I decided to research Local Union records in an attempt to identify members, both active and retired, who had died."

Using notification letters provided by the employer upon the death of any union member, the local union president developed a comprehensive five-year list of every employee who died between 1 January 74 and 31 December 78. With this list of deceased members, he collected from public records all 225 death certificates for analysis.

Based on his subsequent calculations, "the alarming fact that cancer was the leading cause of death among employees" was determined and it was concluded that this evidence indicated "abnormally high cancer death rates."

It was recommended that a positive approach to correcting the situation must be initiated immediately, calling for strengthened plant maintenance programmes, installation of new air cleaners, a programme to identify known carcinogens and to educate employees about their hazards, yearly physical examinations, and a series of follow-up investigations.

Within days copies of the letter and report were in the hands of the employer, the State Department of Public Health, NIOSH and several newspapers. A story in the Detroit News was headlined "Metal plant a cancer suspect." It stated that "A UAW local president who has spent more than a year pouring over death certificates and mortality tables has submitted a report that contends that cancer deaths among workers at....a metal hardware and seat belt plant here may be twice the national average."

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* By Michael Silverstein, 1983; revised 1985.

216

Question 1

a) If you had been the State Health Department representative assigned to investigate this situation, what course of action would you have taken? Who are the interested parties with whom you would need to talk?

b) How would you go about establishing lines of authority, channels of communication, and areas of responsibility?

PART 2

For each of the 225 death certificates in the study, the cause of death had been coded into 15 categories. Cancer deaths were further coded by specific site. The proportion of deaths in each category was calculated and presented for the group as a whole, as well as separately for subgroups defined by sex, race and year of death. For example:

Immediate cause of death by category
total deaths = 225

Cause	Number	Percentage
Cancer	82	36.4
Heart disease	78	34.7
Alcoholism/cirrhosis	13	5.8
Hypertension/stroke	9	4.0
Pneumonia	9	4.0
Suicide	8	3.6
Emphysema	6	2.7

Immediate cause of death by cancer site
male, total subjects = 61

Site	Number	Percent
Lung	27	44.3
Throat	7	11.5
Prostate	5	8.2
Pancreas	5	8.2
Stomach	4	6.6
Lymphatic	2	3.3

Question 2

a) This portion of the local vice-president's analysis is conceptually similar to one of the standard methods in occupational health epidemiology. What type of analysis is this?

b) How might an epidemiologist have approached this differently?

The approximate average yearly number of active and retired union members between 1974-1978 was determined. Using this as an estimate of the number of workers at risk, the annual death rates were calculated by sex per 100 000 persons for all causes of death, all cancer and ten specific cancer sites. These were compared with US national rates for 1974-1975. For example:

Death rates per 100 000 population - males

Cause	US rates 1974-1975	Estimated union rates 5 Year average	Ratio
All causes	890	1184	1.3
All cancer	159	432	2.7
Lung cancer	51	142	2.8
Throat cancer	5	37	7.5
Prostate cancer	14	26	1.9
Stomach cancer	7	21	3.0

Question 3

a) This portion of the local Union analysis is conceptually similar to another of the standard methods in occupational health epidemiology. What type of analysis is this?

b) How might an epidemiologist have approached it differently?

Question 4

a) Do you agree that positive action "must be initiated immediately?"

b) Was there sufficient evidence to act on the local Union's specific recommendations?

c) What would you have proposed?

Here is the way that two different scientists reacted to the report:

a) Dr. X. said he has problems with the study because it does not contain enough detail and back-up information. He said "there may also be problems with some of the comparisons.... The study also does not take into account facts relevant to the incidence of cancer, such as smoking, diet or family history."

b) Dr. Y. said, "There are, to be sure, several technical and methodological problems with the report, but basically it is right on the mark. There is no question that we need to give it serious and prompt attention.... Whatever happens to this situation, we should not lose sight of the initiative, creativity and skill..."

218

Question 5

Which of these comments most closely reflects your own responses to the situation as it has been presented and why?

Copies of the 225 death certificates were provided to the UAW Health and Safety Department and to the Michigan Department of Public Health so that the calculations could be checked and refined.

Question 6

a) What kind of analysis could have been done most quickly?

b) What other analyses might have been considered?

PART 3

The UAW decided to conduct a proportionate mortality analysis. The study group was precisely defined; as all those hourly employees and retirees with at least ten years of credited pension service in the plant who died between 1 January 1974 and 31 December 1978. The union death roster was checked against the company records in an effort to verify the completeness and accuracy of the study group, which ultimately numbered 238.

Death certificates were coded for underlying cause of death by a nosologist. The company provided job history records which were used to determine the total years of plant service and the time between hiring and death for each decedent.

The numbers of deaths from specified causes for groups defined by sex, race, age, and year of death were determined. These were compared with the numbers of deaths expected, based on the total number of deaths and the proportions due to each cause in US national and state mortality statistics. Some of the key findings were as follows:

	Proportionate mortality: white men			
Cause	Observed number	Expected percentage	Expected number	Proportionate mortality rate
Heart	62	0.39		
Stroke	9	0.06		
Respiratory	14	0.06		
Digestive	10	0.05		
Accidents	10	0.08		
All cancer	53	0.23		
Cancer, lung	28	0.09		
Cancer, larynx	2	0.004		
Cancer, stomach	4	0.009		
Cancer, pancreas	3	0.013		
Total	172			

Question 7

a) Calculate the expected number of deaths and the ratio of observed/expected in each category.
b) What do the findings tell you about disease occurrence in this plant?
c) What don't they tell you?

Proportionate mortality ratios were also determined for lung cancer among white males according to the length of plant service and according to the length of time between hire and death:

Proportionate mortality (PMR) by years of service lung cancer - white males

Years	Number Observed	Number Expected	PMR
0-14	10	6.06	1.65
15+	18	8.62	2.09

Proportionate mortality by years since hire lung cancer - white males

Years	Number Observed	Number Expected	PMR
0-22.4	16	8.98	1.78
22.5+	12	5.70	2.11

Question 8

a) How do you interpret these results?
b) Do they support the hypothesis that there is a work-related cancer excess in this plant?
c) Do they confirm this hypothesis?

Question 9

a) What is the "healthy worker effect?"
b) Could this explain the apparent excess in cancer mortality?
c) What would argue for and against such an explanation?
What quantitative method is available which might shed light on this?

Question 10

The proportional mortality results tell us nothing about the mortality rates among the population at risk. What epidemiological method might be used to determine this? Similarly, the proportional mortality results tell us nothing about the association of cause-specific mortality with particular work experience in this plant. What methods might be used to examine this?

PART 4

The study plant was built in 1953 to manufacture small hardware and trim components of automobiles. During the 1950s and 1960s these parts were largely made of zinc, alloyed with 4% aluminum in floor furnaces. Molten metal was transferred to die casting machines and injected under pressure into steel dies. The cooled castings were then trimmed, buffed and polished prior to electroplating with successive applications of copper, nickel and chrome. Since 1971 other operations, including urethane plastics fabrication, had been substituted for much of the plating and die casting.

The plant was one of the world's largest plating and die casting facilities with peak employment of 7500 hourly workers in the late 1950s, dropping to an average of about 3300 since the late 1960s.

Union records show that workers had expressed concern over the years about the mists generated by the plating operations and the smoky emissions released from die casting machines when hot metal hit lubricants and hydraulic oils. There had been very little engineering control of these exposures until the late 1960s when local exhaust ventilation, machine enclosures and mechanization began to be gradually added.

Very little quantitative chemical exposure information was available. Several breathing zone air samples for chromic acid in the 1960s indicated levels from one to five times the current OSHA permissible exposure limit of 100 ug/m^3 in the plating departments. These levels were consistent with reports in plant medical records of chrome ulcers and perforated nasal septa. Several airborne chromic acid levels in 1978 were less than one-half the permissible exposure level.

The UAW conducted a case control analysis to test the possible association of lung cancer mortality with work experience in specific parts of the plant. Lung cancer cases were compared with study population controls, who had died of nonmalignant cardiovascular disease. Cases and controls were examined for length of employment in individual departments. Odds ratios were used to approximate the relative risk of lung cancer mortality for workers employed in those departments where die casting or plating had been done.

For the white males there were three departments for which the odds ratio increased with duration of exposure. The trend was most marked in Department 5, one of the major die casting and plating areas in the plant. The odds ratio of 9.17 for those who worked five or more years in this department was statistically significant. However, the case control findings lacked strong internal consistency. Department 6, for example, was similar to Department 5, yet there was no increasing relative risk with duration of work.

Question 11

There were no walls, partitions or other physical barriers separating one department from another in this plant. How might this have affected the case control analysis?

The UAW concluded that the only responsible course of action given these findings was to consider this study presumptive evidence of a work-related cancer increase until and unless proved otherwise. The union thus requested that engineering controls be improved to reduce all air contaminants associated with die casting and plating, despite the fact that the case control analysis was not completely conclusive and did not identify a specific carcinogen. A voluntary programme of medical surveillance for the early detection of lung cancer was initiated. Chest x-rays and sputum cytology tests were offered to employees following education explaining the medical benefits limitations and risk of these procedures. The company arranged for a research group to conduct a cohort mortality study of this plant.

Question 12

a) Do you agree that the evidence was compelling enough to warrant protective actions for workers.

b) What do you think of the principle of "presumptive action?"

c) Does the fact that recently measured chemical exposures in this plant were within legally allowable limits mean that additional industrial hygiene controls were unnecessary?

Question 13

a) Is early disease detection through sputum cytology testing likely to reduce lung cancer mortality in a high-risk group?

b) Is this type of surveillance warranted if its impact on mortality has not been clearly demonstrated?

INSTRUCTOR'S NOTES

CANCER MORTALITY IN A DIE CASTING AND ELECTROPLATING PLANT

Summary

This exercise describes how members of an automobile workers union recognized an excess of cancer deaths using a proportionate mortality analysis. There are two purposes to the exercise. The first is to encourage students to think about the organizational and political contexts in which public health investigations invariably occur. The second is to illustrate the basic design of a proportionate mortality study, and to stimulate discussion about the merits of different types of study design.

PART 1

Answer 1

a) Before embarking on the scientific work of study design and data analysis, it is prudent to identify and communicate with the persons and organizations who have an interest in the situation. Groups with immediate responsibility for the problem include:

____ Local union (including officers and health and safety representative);
____ International union (both line staff and technical support staff);
____ Plant management (health and safety staff and top administration);
____ Corporate management (both line staff and technical support staff);
____ NIOSH;
____ Federal and State OHSA; and
____ State Health Department (which you represent).

Other parties include:

____ Independent scientific advisors to company and union;
____ Press;
____ Citizen groups in plant neighborhood;
____ Local universities;
____ Local cancer society; and
____ Local tumour registry.

b) In this situation, parties with divergent interests have already been notified. It is unlikely that all, or even a majority of these groups will choose to approach the situation collaboratively. However, lines of communication can be simplified if there is a designated spokesperson for each group. An initial meeting to determine which governmental agency (the State Health Department, NIOSH, or OSHA) will be responsible for the investigation will minimize duplication of effort.

PART 2

Answer 2

a) This, and question (3a) should lead to a discussion of the difference between proportions (which require only a collection of events) and rates (which require knowledge of the population at risk from which the events emerged). The Union's analysis so far is the beginning of a proportionate mortality analysis (PMR). They had collected all deaths, and compared the proportion of deaths due to a specific cause among the autoworkers with the proportion observed in some unexposed comparison population.

b) Although the importance of sex and race were clearly understood in making proportional mortality comparisons, the technique was not used for adjusting for age or calendar year of death in the way that an epidemiologist would have done. Other improvements would be (1) to code underlying rather than the immediate cause of death: (2) to state the proportions in the comparison population and not only the exposed).

In the mortality rate analysis, the epidemiologist would have defined the population at risk to be all those who had worked in the plant at some time in the past, rather than simply the plant population during the years in which the deaths occurred.

Answers 3 and 4

Ask for opinions and reactions from the class. Although there are obviously no "right" answers, it may be possible for the class to reach a consensus that public health decisions can rarely be made on the basis of unambiguous and conclusive scientific evidence and that it is therefore appropriate to make decisive judgements in the fact of uncertainty. Monson (1980), for example, has argued that "whereas opinions as to the meaning of any association seen in epidemiologic data will be varied, action to be taken based on the data must be definitive.... There is no room for equivocation. In the absence of a clear cut interpretation of epidemiologic data, action must be prudent and err on the side of safety."

Answer 5

The replies are meant to generate a list of the major types of studies in occupational epidemiology:

____ Standardized proportional mortality ratio studies,
____ Cohort studies (especially standardized mortality ratio),
____ Case - control studies,
____ Cross sectional morbidity investigations.

Answer 6

PART 3

Answer 7

The completed table should be as follows:

Proportional mortality: White men

Cause	Observed number	Expected percentage	Expected number	PMR
Heart	62	0.39	67.1	0.92
Stroke	9	0.06	10.3	0.87
Respiratory	14	0.06	10.3	1.36
Digestive	10	0.05	8.6	1.16
All cancer	53	0.23	39.6	1.34*
Cancer, lung	28	0.09	15.5	1.81**
Cancer, larynx	2	0.004	0.7	2.86
Cancer, stomach	4	0.009	1.5	2.67
Cancer, pancreas	3	0.013	2.2	1.36
Total	172			

* p 0.05
** p 0.001

Answers 8, 9, 10

Proportional mortality ratios have inherent limitations. For example, a cause-specific PMR can be high although the mortality rate for this cause is low. Also, since the proportions of deaths from all causes must always equal 100%, a deficit from one cause can produce an artifactual increase in another (or vice versa).

Despite these limitations the PMR findings in this study pointed toward a work related cancer excess. The lung cancer PMR, for example, increased with increasing years of service and with increasing years since starting at the firm. These apparent trends should not be over-interpreted. The years of service PMRs of 1.65 and 2.09 are not reliably different from each other; their 95% confidence intervals overlap. Also, PMRs are dependent upon the age distributions of the decedent group and cannot be directly compared with one another, unless these age distributions are similar. These findings, in other words, are consistent with but do not prove a work-related problem.

There is additional indirect support for the view that the cancer excesses are work related in that the data are not consistent with some of the possible non-work etiologies. If, for example, the cancer PMR was elevated simply as a reflection of a lowered mortality from cardiovascular disease in an essentially healthy group of workers, the distribution of cancer among various sites would not be affected. In this group, however, lung cancer deaths were found disproportionately often in comparison with other cancer deaths. A quantitative measure of this is the Proportional Cancer Mortality Ratio.

PART 4

Answer 11

The absence of physical barriers could affect case control findings, if there were airborne carcinogens in the plant which were not confined to specific departments. Under these circumstances the assignment of exposures according to department would result in misclassifications insofar as departments which were treated as unique environments might in fact share exposures. This would push the odds ratios toward a value of one, underestimating any excess relative risk which was actually present. A preferable way to conduct the analysis would have been to assign exposures based on actual measurements of airborne chemicals at various work stations in the plant at specific points in time. This, however, was not possible given the available data, and departmental assignment was used as an imperfect proxy.

Answer 12

Some might argue that the findings from this plant should be considered just preliminary and that additional epidemiology is the only appropriate follow-up. The rationale for such a view might be that a specific carcinogen was not identified, that some of the results were not statistically significant, that the results were not completely consistent, or the conviction that PMRs can only generate hypotheses for subsequent testing.

Another view is that decisions based on any one of these measures should not substitute for looking at the whole picture. Many epidemiologists have suggested that decision making take several factors simultaneously into account. Monson (1980), for example, considers seven criteria to be important in occupational epidemiology:

1. Consistency,
2. Specificity,
3. Strength of association,
4. Dose-response relationships,
5. Coherence (biological plausibility),
6. Temporal relationships,
7. Statistical significance.

Statistical significance, notably, is only one criteria among many and it may be useful to discuss this if there are class members who are particular fond of the "p value." What if, for example, the p value for the lung cancer PMR of 1.81 had been 0.09 instead of 0.001?

The p value is just a number expressing the liklihood of rejecting the null hypothesis when it is actually true. Statistical significance, however, incorporates subjective judgments reflecting the degree of confidence that scientists feel is necessary before being willing to state a conclusion or to recommend action. That these judgments are not immutable scientific truths but embody situational values can be seen by noting certain inconsistencies in decision-making behavior. Many scientists who would never recommend protective actions in a workplace when an observed lung cancer excess was "only" 80% likely to actually be true, would nonetheless carry an umbrella to work if the morning news reported an 80% likelihood of rain.

Answer 13

It has not been established that chest x-rays and sputum cytology can reduce lung cancer mortality even in a high risk group, although survival times might be increased because of early detection of some cases. In fact, there may even be some extra risk associated with the screening programme, because positive sputum cytology tests, including false positives, will often be followed up by bronchoscopy, a hazardous medical procedure. In view of these facts some people would argue that this surveillance should not have been undertaken. The decision was made to present the facts to the employees in this plant and to allow them to make their own choice.

Reference

Monson, R.R. Occupational epidemiology. Boca Raton, CRC Press, 1980, 219 pp.

M

LEUKEMIA IN NUCLEAR SHIPYARD WORKERS*
USES AND PITFALLS OF PROPORTIONAL MORTALITY STUDIES

PART 1

It is 1978, and a Subcommittee on Health and the Environment of the US Congress has just ordered the National Institute for Occupational Safety and Health (NIOSH) to investigate a report of excess deaths from leukemia at a US nuclear naval shipyard. You are assigned to this project.

Concern stems from a recent epidemiological finding that the proportion of deaths from leukemia was 5.6 times higher among workers at this nuclear submarine repair facility than was expected from US age-specific proportional mortality (Najarian & Colton, 1978).

Question 1

What type of study is this? What is the measure of disease (mortality) occurrence that the investigators are comparing between the 'exposed' and the 'unexposed' populations?

PART 2

While tracking down a reprint of this study, you think back on your extensive midnight readings in epidemiological methods and recall that proportional mortality ratio (PMR) studies are frequently controversial because of intrinsic design limitations.

Question 2

a) How does the design of a PMR study make it an intrinsically indirect way to assess the mortality experience of a population?
b) Under what conditions will the results be misleading, even if the study itself is conducted well?

Description of the nuclear shipyard worker study

On reviewing the published report, you find that the investigation of mortality among the shipyard workers was begun and conducted in an unusual manner (Najarian & Colton, 1978). One of the investigators was a hematologist, who in 1977 examined and treated a nuclear shipyard worker with hairy cell leukemia. The patient, a 65-year old welder, had been employed in repairing nuclear submarines from 1959-65. Because of the known association** between ionizing radiation and leukemia (Anderson 1972; Conard et al. 1975; Moden, et al. 1977), the physician wished to determine whether other cases were occurring among fellow shipyard workers. Essentially no information was available on which to base an epidemiological study. Neither the hematologist nor his colleagues had access to personnel, or exposure (dosimetry) records at the shipyard. They did have access to State death certificate information. They elected to review all death certificates for the years 1959-77 in the three States contiguous to the shipyard, and to identify all of the deceased for whom work at the naval shipyard was recorded as the "usual occupation".

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* Michael J. Thun & James J. Beaumont, 1983; edited 1984.
** Further information on this subject was later published by NAS-NRC, 1980.

Question 3

a) Do you agree that a single case of leukemia in a nuclear worker warranted further investigation?

b) Would this method of ascertaining deaths among the shipyard workers provide reliable data for a PMR study?

c) Given the difficulty of obtaining the death certificates, do you feel that a PMR is indicated at all? When are PMR studies useful?

From their review of the State death certificates, the investigators identified 1722 certificates between 1959-77 on which the "usual occupation" or employer was recorded as the naval shipyard. To further classify these deceased workers as "nuclear" or "non-nuclear", they then sought to obtain additional information. This was necessary because only an estimated 20% of the workforce was employed in the nuclear section of the shipyard. They attempted to do this by telephoning the next-of-kin and asking whether the deceased wore a radiation badge. The questions were:

Did you know the deceased?
Did he work at the shipyard?
Did he work with radiation or wear a radiation badge while working?
What was the cause of death?

To encourage participation, a major newspaper ran numerous articles publicizing the study, and urging shipyard workers and their families to participate. Despite this, the telephone interviews were completed for only 592 of the deceased (34%). From this subset, the investigators classified 146 of the deceased workers as being nuclear, and 379 as non-nuclear.

Question 4

What problems might you anticipate from this method of classifying the exposure status of the deceased nuclear shipyard workers?

PART 3

Assuming for the moment that the enumeration of exposed deceased shipyard workers is correct, you continue your review of this study. The information from a number of tables presented in the paper by Rinsky and coworkers (1981) can be condensed into the following format. This shows the number of deaths observed and expected from leukemia, from all cancers, and from all causes among persons classified as 'nuclear' workers.

Number of deaths from selected causes among nuclear workers

	Observed	Expected	O/E
Leukemia	6	1.1	5.45
All cancers	56	31.5	1.78
All deaths	146		

Question 5

How were the number of expected leukemia and cancer deaths computed? How do these relate to our previous discussion about the PMR being a comparison of proportions?

In actuality, the number of expected deaths was computed in a more complicated way, stratifying for age and calendar year in which the death occurred. Although we do not have the data from the original study, we can illustrate this using some invented data for white males from two time periods and three age groups.

Example - computing a PMR

(A) Total number of deaths observed among the exposed

Age (years)	Year 1960-64	Year 1965-69
20-24	10	5
25-29	10	15
30-34	5	5

(B) Proportion of deaths due to cancer in the referent population in corresponding age and calendar periods

Age (years)	Year 1960-64	Year 1965-69
20-24	0.07	0.07
25-29	0.09	0.10
30-34	0.11	0.12

231

(C) Number of observed and expected deaths due to cancer among the exposed

Age (years)	Year 1960-64 Obs.	 Exp.	 1965-69 Obs.	 Exp.
20-24	2	___	1	___
25-29	3	___	4	___
30-34	0	___	1	___

Summary PMR ___

Question 6

a) What is the purpose of this complicated scheme?
b) Compute the numbers of cancer deaths expected for each cell of the matrix and the PMR?

PART 4

Although you are quite confident that the findings of the initial PMR study are unreliable, there is intense public pressure on both NIOSH and you to determine whether adverse health effects due to radiation are occurring at the shipyard. The commanding officer of the naval base indicates that he is willing to cooperate with an epidemiological study, provided that you can tell him what you intend to do and why.

Question 7

Given this setting, what type of study would you propose, and why?

PART 5

To evaluate whether radiation exposures at the nuclear shipyard have caused an excess of deaths from cancer, you and your colleagues undertake a retrospective cohort mortality study of all workers ever employed at the same naval shipyard between 1952-1977 (Rinsky, et al. 1981). You identify 7615 civilian workers who meet these eligibility requirements, and determine their vital status and causes of death up to 15 August 1977. According to film badge records maintained by the Navy, these workers received between 0.001-91.414 roentgen equivalent man (rem) of external radiation exposure.

One of the analyses from the cohort mortality study is comparable to the data in the PMR study. The results show:

Observed and expected deaths among 7615 white male shipyard workers
(Recorded lifetime cumulative radiation dose of at least 0.001 rem)

Cause of Death	Observed	Expected	SMR	95% CI For SMR
All causes	833	1065.3	78	73 - 84
All cancers	201	218.5	92	80 - 106
Leukemia	7	8.3	84	34 - 174

Question 8

a) How do the results of this retrospective cohort mortality study compare, or conflict with the results of the previous PMR ratio? Which do you find more believable?

b) Another 1345 workers were identified, who were selected for radiation work but never received documented exposure. The PMR study might have classified these workers as 'exposed' had they worn radiation badges. Would inclusion of these nonexposed workers in the exposed group lead to under- or over-estimation of a true relationship between radiation and leukemia?

Concluding remarks

This brief discussion is intended to illustrate several fundamental points about the proportionate mortality study, and not to attempt to recapitulate the complexity of events and issues with regard to each of the studies discussed. For a fuller appreciation of these papers, the reader is referred to both the original articles (Najarian & Colton, 1978; Rinkly, et al. 1981) and to a full discussion of the biases involved (Greenberg, et al. 1983).

In addition, discussion of the original PMR study is intended for teaching purposes only, and not to present a too critical attitude towards the actual study. Out of this study evolved an opportunity for more extensive and detailed evaluation of the health consequences of nuclear shipyard work.

Acknowledgements

The ideas presented in this teaching case are the product of numerous discussions contributed to by unacknowledged participants. Dr. Richard Monson used these papers as teaching examples in a course on occupational epidemiology at the Harvard School of Public Health. Dr. Robert Rinsky, the author of the follow-up study, also offered many valuable suggestions during the preparation of this case study.

M 7

USES AND PITFALLS OF PROPORTIONATE MORTALITY STUDIES
INSTRUCTOR'S NOTES

Summary

This case study illustrates a number of features (both advantages and limitations) of proportional mortality (PMR) studies. These include:

1) That PMRs compare proportions rather than rates;

2) That proportions are an indirect measure of disease occurrence, and that special conditions must be met for the results to be unbiased;

3) That, because of these intrinsic design limitations, PMRs are chiefly useful for hypothesis generation;

4) That PMRs are frequently performed as a 'first cut' exploratory study, because of their simplicity and expediency; and

5) That either cohort mortality/morbidity studies, or nested case control studies are usually used to attempt to verify or refute the findings of a proportional study.

PART 1

Answer 1

This is a proportional mortality study. The measure of disease occurrence is the proportion of all deaths due to a specific cause, rather than the incidence (or mortality) rate from that disease. The ratio of this proportion in the exposed and unexposed populations is called the proportional mortality ratio (PMR) (Monson, 1980). The use of proportions to compute the PMR can be expressed symbolically as:

		Exposed		Comparison
Cause-specific deaths		d_1		D_1
All deaths		d_n		D_n
Proportion of deaths due to a specific cause	$P_1 =$	d_1/d_n	$P_0 =$	D_1/D_N

$$PMR = \frac{P_1}{P_0} = \frac{d_1/d_n}{D_1/D_n}$$

The proportionate mortality ratio is the ratio of these two proportions (exposed/unexposed) and is used to estimate the effect of exposure upon mortality. A side-issue that the class may wish to discuss is that the US or the State general population is often used as the "unexposed" population, and that these reference populations are neither unexposed, nor are they necessarily comparable. Both criticisms are true. These limitations are not specific to PMR studies, nor are they directly related to the logic of this problem. The rationale for using the general population is that it is is large enough to provide stable rates, and that the number of "exposed" persons is small, relative to the overall population.

PART 2

Answer 2

a) This question is both theoretical and practical. The PMR is an indirect means of comparing the mortality experience of two populations (exposed versus unexposed), because it is not based upon death rates. Rates, defined as deaths from specific causes per person-time at risk, are the preferred measure of mortality, just as the ratio of these death rates (exposed/unexposed) is the preferred way to compare two populations (Kleinbaum, et al. 1982). Such a "rate ratio" would look like this:

	Exposed	Unexposed
Number of cause-specific deaths	d_1	D_1
Person-time at risk	pt	PT
Cause-specific death rates	d_1/pt	D_1/PT

$$\text{Rate ratio} = \frac{d_1/pt}{D_1/PT}$$

In a PMR study, the investigator lacks information about the number of person years at risk, and attempts to use deaths (numerator data) to estimate the rate ratio. This introduces two potential problems (see answer 2b) below).

2b) The PMR will be misleading: (1) when the all-cause death rates in the two populations are unequal, or (2) when a single very common cause of death is substantially elevated or depressed. The reason for the first can be shown algebraically, but it can be illustrated by a simple, although improbable, example. If an exposed population has death rates that are exactly twice those of the comparison population for all causes of death, then each cause-specific PMR would equal 100 (i.e. no effect) even though all of the death rates are twice that expected.

The second problem can also be explained simply. Because all causes of deaths must add up to 100%, a large increase or decrease in any common cause of death will lower or raise the proportionate contribution of other causes of death. Proportions, unlike rates, are not independent of each other. This causes a practical problem in workplaces where the "healthy worker effect" results in a lower than expected death rate from cardiovascular disease. The lower than expected number of deaths from cardiovascular disease can cause the proportion of deaths from cancer to appear to be elevated. (Note- This "healthy worker effect" may occur because, in many occupational settings, the physical demands of working select for workers who are healthy enough to apply for employment and be hired.)

Answer 3

a) Opinions may differ on this. Although leukemia in males occurs at a background rate of approximately 8 per 100 000 person-years, leukemia in a radiation worker should be considered a "sentinel event". The recognition of any type of leukemia (except for chronic lymphocytic) in a radiation worker should arouse concern that radiation may have been responsible.

The extent of one's investigation is then dependent upon the presence or absence of other cases, the question of whether the latency period since first exposure makes a causal relationship biologically plausible, the likelihood of substantial radiation exposure, given the patient's occupational history, etc.

b) This method of ascertaining deaths among the shipyard workers is a poor one, first because it is remarkably difficult, and second, because it is unlikely to provide a complete or unbiased roster of deaths among the shipyard workers. To be valid, a PMR must be based upon all deaths, or at least a representative sample of all deaths. In this instance, the physicians or funeral directors who filled out the death certificates might have been more likely to note the nuclear shipyard work on the death certificates of those persons for whom they suspected an occupational etiology for the death (e.g. for persons dying of leukemia, other cancers, or on-the-job accidents). Thus, this method of identifying the shipyard workers might have selectively ascertained certain types of death, out of proportion to other types, potentially biasing the PMR.

Alternatively, only ascertaining deaths in the three adjacent States might selectively miss workers who stopped employment and migrated because of certain causes of death. Although neither of these potential selection biases can be proved, they cannot be ruled out with certainty.

c) The difficulty of obtaining the death certificates in this setting eliminates the two major advantages of PMR studies, namely convenience and speed. The usual setting in which PMRs are conducted is that in which numerator data (deaths, or incident cases) are immediately available, whereas denominator data (person-time at risk) can be determined only with great difficulty. For example, the union or company might have a file drawer containing the death certificates of all deceased employees who participated in an insurance pension plan. Such records can be used epidemiologically, provided that the file is complete, or at least representative of all deaths. Although not definitive, a PMR based on such a file can be used to quickly support or weaken a subjective preliminary impression that some cause of death is occurring in excess. If the excess involves some unusual, "sentinel" tumour, such as angiosarcoma of the liver among vinyl chloride workers, or mesothelioma among asbestos-exposed workers, the evidence may be quite convincing. Immediate public health action is justified in such cases, based on the PMR results alone. More often, PMR results show a smaller excess of a more common cause of death, and are useful for hypothesis generation.

A different setting in which the PMR method is useful occurs when the investigator has access to registry data (either tumour incidence or death certificates) and wishes to generate hypotheses about industries or occupations at high risk of specific diseases. In this setting, the same proportional technique is used to identify those causes of death for which certain occupations or industries contribute an unusually high proportion of the cases. This surveillance technique is useful to generate new hypotheses. When based upon morbidity or disability data, the result is still called the PMR, meaning proportional morbidity ratio.

Answer 4

None of the numerous problems of this method are specific to PMR studies. The two biggest problems are 1) the potential for selection bias, since only 34% of the deceased were included in the study and 2) the potential for differential misclassification of exposure. It is quite possible that the telephone interviewers were the more persistent in contacting and interviewing the next of kin of persons dying of cancer and leukemia. Alternatively, the families of persons dying of these diseases may have been more responsive to the newspaper articles and may have contacted the interviewers. Similarly, the family respondents may have been more likely to report radiation work, if the deceased died of a cause which they believed was related to radiation. These problems go well beyond those which are intrinsic to the PMR.

PART 3

Answer 5

The answer is included in the text of Part 3 (pages M 3-4).

Answer 6

While conceptually the PMR is simply the comparison of two proportions, in practice it is the comparison of observed deaths from a specific cause to the number expected, where the expected number of deaths is derived from the proportion in the "unexposed". Mathematically:

$$PMR = \frac{P_1}{P_0} = \frac{d_1/d_n}{D_1/D_n} = \frac{d_1}{D_1 d_n/D_n} = \frac{\text{Observed}}{\text{Expected}}$$

The expected is calculated by multiplying the proportion of deaths due to cause D_1 in the reference (comparison) population times the total number of deaths in the "exposed". The actual calculations compute the expected for specific subgroups of age, calendar year, race, and sex, and sum the results leading to a standardized PMR. This point will be illustrated in the answer 6a below.

a) The purpose is to control for the potentially confounding effects of age, and calendar year without having to divide an already small data set into even smaller subgroups. The technique of stratifying and then standardizing allows one to develop a summary PMR for all persons of the same sex and race.

b) Number of observed and expected deaths due to cancer among the exposed

	Year			
	1960-64		1965-69	
Age	Obs.	Exp.	Obs.	Exp.
20-24	2	0.7	1	0.35
25-29	3	0.9	4	1.5
30-34	0	0.55	1	0.6

Summary PMR =11/4.6 = 2.4

(Note, these data were invented, and do not apply to the nuclear shipyard workers)

PART 4

Answer 7

Given the level of public concern, only a definitive study will convincingly confirm, or refute the previous findings. The two most likely choices would be either a retrospective cohort mortality study, or a "nested" case-control study. The latter would involve a case-control study, nested within the population of shipyard workers, to compare the occupational and non-occupational histories of all cases of leukemia at the shipyard, with equivalent histories in a non-leukemic reference group.

Since both the cohort and the nested case-control studies will require follow-up of vital status on the entire cohort of shipyard workers, the retrospective cohort approach seems the best first step. (Other choices, such as cross-sectional surveillance of white blood cell counts in the radiation workers, or repetition of the PMR study including all deaths, are unlikely to provide a definitive answer.)

PART 5

Answer 8

a) It is clear that, at least in the overall analysis (disregarding dose) the cohort mortality study shows no evidence of excess mortality from either leukemia or all cancers. It is still possible that this overall analysis could be missing an effect among the more highly exposed subgroup of workers. However, this analysis is most comparable to the original PMR study, and shows no increase of deaths from leukemia. Thus, the apparent 5.6-fold increase of leukemia deaths in the PMR was due to one or several of the biases discussed above.

There are really two components to this question. The first concerns the quality and care with which an individual study is conducted. As mentioned above, the original PMR is particularly vulnerable in this area. The second issue concerns the intrinsic strength of study design. All other quality control factors being equal, a cohort mortality study is always more convincing than a PMR.

b) Such misclassification of exposure would cause an underestimation of a real effect.

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241

MINING, SMOKING AND LUNG CANCER
PROBLEMS OF INTERACTION AND QUANTIFICATION OF RISK*

Introduction

A high lung cancer mortality among miners was reported from Central Europe in the 19th century. In the 1920s is was suggested that radioactivity in the air, called "radium emanation" at the time, was etiologically responsible. This radium emanation was later recognized as radon and short-lived radon daughters in the air, i.e. decay products from uranium through radium, the radon daughters being isotopes of bismuth, lead and polonium.

In the 1960s and 1970s several reports indicated a similarly increased lung cancer mortality both among uranium miners and other miners in many countries, e.g. in Canada, France, Sweden, the United Kingdom and the United States of America. Work in coal and salt mines usually low in radioactivity, has not been associated with any excess of lung cancer, however.

There has been quite a debate over the years about the epidemiological findings of lung cancer among miners, especially regarding the US uranium miners. A quotation from B. MacMahon in 1971 could be an illustration in this respect: "The epidemic of lung cancer now in progress among American uranium miners could readily have been - and indeed was - predicted on the basis of past experience in other parts of the world .... Although .... few comparable medical experiences have been so carefully documented, diametrically opposite opinions are still held and expressed not only regarding the interpretation of the facts that have emerged, but also to the nature of the facts themselves".

PART 1

Further studies and new questions

When it became increasingly clear in the late 1960s and early 1970s that radon daughter exposure in mines was the probable cause of the excess lung cancer mortality seen among miners, attempts were made to quantify the lung cancer hazard by comparing the experiences from different mining populations. However, quite discrepant estimates were obtained with regard to the quantified risk, ranging from 6 to 47 excess lung cancer cases per 10^6 person years and working level month (WLM, i.e. an alpha radiation dose unit, one WLM referring to a month (or 170 hours) of exposure to the concentration of one WL). One WL is any mixture of short-lived radon daughters, that would release a quantity of alpha radiation energy amounting to 1.3×10^5 Mega electron Volt (MeV) through its complete decay through radium C', the last one of the short-lived daughters or polonium-214.

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* By Olav Axelson, 1985; revised 1985.

However, the various studies of miners and lung cancer have resulted in somewhat contradictory findings with regard to the effect of radon daughter exposure in connection with smoking. The first studies of uranium miners suggested a multiplicative interaction, but later studies from various types of mines showed that non-smokers were at considerable risk as well. Furthermore, several studies have also indicated a less than multiplicative interaction between smoking and radon daughter exposure, and two small scale studies of old, mature mining populations have even shown more lung cancers among non-smokers than among smokers. This finding was unexpected but actually fitted in quite well with some theoretical calculations of the alpha radiation dose to the epithelium, since smoking should be expected to cause increased mucous secretion and decrease the effective penetration of the short-ranging alpha radiation to the basal cells of the epithelium (Altshuler, et al. 1964). Hence, the distance from the surface of the mucous layer down to the basal cells of the epithelium is critically long for the alpha particles to the able to penetrate, so a thickening of the mucus layer would tend to reduce the effective dose of alpha radiation to the epithelium. Interestingly even some animal experiments with beagle dogs have gone in this direction, i.e. the ones who smoked got fewer cancers than the non-smokers (Cross, et al. 1942).

Furthermore, judging from some of the studies of various mining populations, the induction-latency time from first exposure to radon and daughters until the development of lung cancer seems to be shorter for smokers than for non-smokers, even when the latter had a lung cancer risk as high or even higher than the smokers. In one of the studies this induction-latency period was reported to be very long, i.e. 37 years on the average for smokers and 49 years for non-smokers (Axelson & Sundell, 1978). However, all the studies were not quite consistent with each other and some of them did not show any difference in induction-latency time between smokers and non-smokers (Archer, et al. 1973; Dahlgren, 1979).

Question 1

What questions (or hypotheses) about radon daughter exposure would be of interest to focus on from a scientific point of view?

Question 2

Further studies would obviously be of interest but what sort of populations would be needed for elucidating these questions (hypotheses)?

Question 3

What sorts of epidemiological approaches would be applicable to obtain an answer to the questions as formulated above?

PART 2

A population for study

Mining in Sweden has been going on for more than a thousand years. For the last century or so, many mines have been in operation, but most of them were relatively small in terms of the working population, say, about a hundred individuals or less. Most of these mines have been closed during the last two or three decades, and it would consequently be difficult to obtain information both regarding the population and the work conditions. By the time of the study, four larger mines were in operation in Sweden, but only one of them had not yet studied with regard to the lung cancer risk, namely the mine at Grängesberg in southern, central Sweden.

The Grängesberg mine. Mining iron ore has been in operation at Grängesberg for several hundred years. By 1910 the open pit mining had reached depths of 70-100 metres and underground mining had started. The ventilation was "natural" until 1945 when the mine was still rather shallow. Then, mechanical ventilation was introduced and further changes in the ventilation technique took place in 1955-56, when air was taken down through old shafts and transported underground to gain heat from the ground in winter time so as to hinder freezing of water in the mine. The dust levels in the mine were reduced considerably through this new ventilation but at the same time, the air was probably more contaminated by radon due to the prolonged transportation time underground for the ventilation air.

In 1969, diesel-driven equipment was introduced and the ventilation had to be further improved for this reason as well as because of emerging concern about radon. Consequently, the ventilation was improved through two new, vertical ventilation shafts and reached a capacity of 1 350 000 m^3/ hour, which also reduced radon and radon daughter levels.

Potentially hazardous exposures, other than to radon and radon daughters, may occur in a mine, since the atmosphere tends to be quite complex. For example, there could also be other, more or less well-established carcinogens present such as arsenic, nickel, chromium, asbestiform minerals and diesel exhausts. The iron ore at Grängesberg is known to contain only small traces of nickel and chromium, however, and there is no indication of any pertinent occurrence of asbestiform minerals.

Information on exposure and subjects. The first measurements of radon daughter levels were made in 1969-70 and showed levels of about 0.3-1.0 WL. With the new ventilation installed in 1970, the present levels of radon daughter exposure were reduced to about 0.3 WL or less.

Sweden has a well-tried system for the central registration of cancers and a local as well as a central registration of deaths based on death certificates. There is also a continuously updated register of the living population. Regional and local population registration takes place on several levels with the parish as the smallest unit. All births and deaths are registered for each parish and there is a continuous update of the register of persons living in the parish. For historical reasons, population registration has been conducted by the church for over two hundred years.

The mining community of Grängesberg has had about 3000 inhabitants in the parish. The registration of deaths in the parish is in a book with a continuous list for each year, quoting information from the death certificate and usually also adding an occupational title.

There has been an outpatient health care unit at Grängesberg for a long time and more recently also industrial health care facilities for the mine, mainly dealing with work-related diseases and prevention. The hospital for the area is located relatively far away. Other circumstances relevant to data acquisition might be that the mining company, like most companies in Sweden, has had a fairly good administration and a careful registration over many decades of their employees. In Sweden it is usually possible to cooperate with a company to obtain information about, for example, the employment dates for an individual. Sometimes there is salary information as well, paid for particular work tasks. The costs involved in going through the registers could be relatively high, especially considering the comparatively high Swedish salaries. It should also be mentioned that the population is usually quite cooperative in answering questionnaires and interviews, which of course facilitates certain types of epidemiological studies.

Question 4

Considering the information given, what epidemiological approaches would be possible and preferable? What would be the main points in a preliminary study protocol and what specific problems might be anticipated for the study?

PART 3

The register of deaths at the parish of Grängesberg was consulted for the somewhat aribitrarily chosen period of 1957 to 1980 and 57 males were found to have died from lung cancer. During the first part of the study period there was a relatively steep increase in the annual number of lung cancer deaths followed by a levelling off at about 1966 (Table XXIX).

Table XXIX. Male lung cancer deaths per three year periods in the parish of Grängesberg from 1957 to 1980

Time period	Number of lung cancer deaths among	
	Miners	Others
1957-59	1	-
60-62	1	-
63-65	6	-
66-68	8	-
69-71	8	2
72-74	8	1
75-77	10	2
78-80	10	-
1957-80	52	5

The study period had to be restricted in time to the years 1966-1977 for several reasons: 1) The ventilation changes in the mine. 2) Increasing number of lung cancer cases per year until the later 1960s. 3) Some practical and economic reasons (having to do with the time from starting the study in 1978 to its termination in 1981). Not only lung cancer but also all other deaths were noted for the males ages 50 years and older in the parish for this period. From the general population statistics of Sweden, it was also possible to obtain information about the total male population in the parish with regard to age group. Average figures for the period are shown in Table XXX along with the number of lung cancer cases and other deaths in the parish.

Table XXX. Male lung cancer deaths and other deaths in the parish of Grängesberg during 1966-1977, along with figures for the average male population. (Note that radon daughter exposure does not seem to cause any particular excess of conditions other than lung cancer among miners).

Ages	Lung cancer deaths		Other deaths		Average total population
	Miners	Non-miners	Miners	Non-miners	
50-65	13	3	38	66	669
> -65	20	2	145	254	477
Total	33	5	183	320	1146

Question 5

What sort of population do these data refer to? What sort of epidemiological study designs might be applicable?

Question 6

Calculate crude and weighted (standardized) relative measures for the miners to get lung cancer in comparison to the general population (along with a confidence interval).

PART 4

Since smoking is a strong determinant of lung cancer, it is usually necessary to take care of smoking in one way or another if lung cancer is studied epidemiologically. In this particular investigation interviews with regard to smoking were made with the relatives of the lung cancer cases, as well as with the relatives of a sample of other deceased miners with other causes of death than malignancies. Because of the possibility that not only lung cancers but also other malignancies depend on smoking, other malignancies were excluded. For the same reason one could think of excluding cardiovascular deaths as well to obtain good representativeness of the study population through the referents (controls), although this was not done here.

These other deaths were chosen to have about the same ages (up to ± 6 years difference in the year of birth) and the same year of death (up to ± 2 years difference) as the lung cancer cases. The information obtained from these interviews is summarized in Table XXXI. It was possible to find a referent for 28 of the lung cancer cases and to obtain full information both from the case and from the referent.

Table XXXI. Information on smoking habits of 28 lung cancer cases and their fellow work-mates, who died from other causes (+ means smoking, non-smoking). Each case along with the matched referent is given a serial number.

Serial numbers	Lung cancer deaths	Other deaths
1	+	+
2	+	+
3	+	+
4	+	+
5	+	+
6	+	+
7	+	+
8	+	+
9	+	-
10	+	-
11	-	+
12	+	-
13	+	+
14	+	+
15	+	+
16	+	-
17	-	+
18	+	-
19	+	-
20	-	+
21	-	+
22	+	+
23	-	-
24	+	+
25	+	+
26	+	+
27	+	+
28	+	+

Question 7

For presentation of data it is commonplace to condense information from a table like Table XXXI. The following scheme is suitable for this purpose; give the number of pairs (not individuals) in the various cells: -

Smoking habits in the 28 matched pairs of underground miners.

	Referent	
Case	Smoker	Non-smoker
Smoker	?	?
Non-smoker	?	?

Question 8

Evaluate the effect of smoking in the causation of lung cancer in miners by calculating the rate ratio (odds ratio) from the table constructed above. Apply also a significance test for matched data and obtain test-based, approximative confidence limits.

Question 9

As seen from the above calculations the rate ratio is as low as 1.5. What conclusions might be drawn from this finding?

PART 5

Some other information of importance was also gathered in the course of the study, namely that those non-smokers among the miners, who died from other causes than lung cancer, had been employed underground for 25.7 years and the smokers had 26.9 years of employment. The time underground for smoking lung cancer cases was 29 years and 29.4 years for the non-smoking cases. The exposure time for the 13 cases aged 50-65 years was found to be 27 years and 30.4 years for the 20 cases of 65 years and above. Furthermore, it may be remarked that vacation time, sickness leave etc. might be taken as a month per year with regard to the time period of exposure.

Question 10

Estimate the number of miners that on an average had been employed within the study period of 1966-77, also considering age-groups.

Guidance: Look at the distribution of miners and non-miners among "other deaths" in Table XXX and divide up the total population accordingly.

Question 11

Estimate the number of excess lung cancers per WLM and 10^6 person-years in ages 50-60 and > 65 years.

Guidance: As a result of question 10 the number of cases per person-years can now be easily obtained for miners and non-miners. The dose in WLM has to be estimated through the cases (as has been traditionally done, although the cases might not be fully representative for the population to which they belong).

Question 12

Discuss in what particular respects there may or may not be systematical errors (bias) in the study?

Question 13

What conclusions can be drawn from the study and with what degree of certainty?

Finally it may be remarked that the answers to these various questions are more or less directly available from the published paper about this investigation (Edling & Axelson, 1983).

INSTRUCTOR'S NOTES
MINING, SMOKING AND LUNG CANCER
PROBLEMS OF INTERACTION AND QUANTIFICATION OF RISK

This case is based on a study that has been published (Edling & Axelson, 1983). The questions refer more or less directly to the information provided in that article, which the teacher should read. On purpose, relatively little guidance has been given to the students. It is left to the teacher to give further help and information, obtainable from the original publication and from the notes below. The teaching objectives of this case are: 1) An opportunity for the advanced student to choose among alternate epidemiological methods. 2) An opportunity to calculate the appropriate estimates of risk and rate. 3) An opportunity to interpret complex epidemiological data. The answers to the questions along with some comments follow:

PART 1

Answer 1

Further quantification of the lung cancer risk from radon daughter exposure is needed.

The character of the interaction of smoking and radon daughter exposure seems to be complex and deserves further study, i.e. there could be both a protecting effect from an increased mucus layer due to smoking which could lead to decreasing the radiation dose, and also a promotion effect of smoking on cancer once it has been induced, especially as the smokers were found to have shorter induction-latency times in some studies.

Answer 2

Rather old and mature populations would be needed to observe the appearance of lung cancer especially among the non-smokers, whereas the lung cancers would be expected to appear earlier among the smokers. Preferably extinct subpopulations should be studied, i.e. those born some 90 years ago or earlier.

Answer 3

In principle one could think of both cohort and case-referent approaches. It would be difficult however to define a cohort sufficiently long ago (preferably about 60-80 years ago if it should be extinct or almost extinct at the time of the study). Therefore, a case-referent approach would be easier, even if, again, it is difficult to obtain exposure information so far back in time as around the first two or three decades of this century).

Perhaps it would have been possible to utilize the registers of the company to establish a cohort from the 1920s or 1930s, but certainly it would have been a quite laborious task. A proportional mortality study, or alternatively, a case-referent design seemed preferable, therefore. The local register of deaths would be the most efficient source of subjects.

(There was no good alternative since no hospital was located in the parish and the out-patient unit would not have any effective registers.) The referents could not be continuously drawn from the population register over the study period i.e. contemporary with the appearance of the cases, since the register had been continuously up-dated with deaths being deleted. Therefore it was necessary to utilize other dead cases as referents, i.e. either a proportional mortality study or a case-referent study could be chosen; the authors preferred the latter; cf 1).

PART 2

Answer 4

A preliminary study protocol should deal with the following aspects:

1. Cases are those with lung cancer as obtained from the register of deaths in the Grängesberg parish.

2. Referents are those dead from other causes in the same parish and time period. Other cancer deaths could have the same exposure background and etiology as lung cancer cases, especially there could be a relation to smoking, but earlier studies on miners with radon daughter exposure do not suggest any other definite and job-related cancer hazard than lung cancer (Axelson, 1979).

3. Smoking habits might be found out through interviews with relatives (the addresses of whom would be obtainable through the population registration of the parish.) Mailed questionnaires or interviews could be considered (the latter approach was chosen, especially as it was possible to engage a couple of former foremen for this task) (Pershagen & Axelson, 1982).

4. The smoking evaluation might be limited to miners only in a comparison of the lung cancer risk of smoking and non-smoking miners. Matching of the cases to the referents on age could be thought of as preferable in the design (but random referents of miners would also do with a subsequent stratified analysis).

5. Lists of subjects (cases and referents) could be given to the company (without revealing status of case or referent) for identification of those who were ever employed underground along with information on time in underground work.

6. Dose-estimations to be made from available data on radon daughter concentrations in the mine (0.5 WL was finally assumed as the most likely average level).

7. Statistical calculations might be based on the Mantel-Haenszel procedures (1959) and the Miettinen principles (1972) for the confidence interval calculations and standardization. The McNemar test could be applied for matched pairs when considering the effect of smoking.

8. Information about the size of the general population would provide also for calculations of excess cancers per WLM and 10^6 person-years (note that the referents would represent the population of miners and non-miners in the various age-groups; Miettinen, 1976).

Problems to be anticipated are the estimation of dose and obtaining correct information on smoking, whereas other information might be thought of as quite correct as based on the company's files.

PART 3

Answer 5

This is an example of an open population, i.e. with a turnover, in contrast to, for example, an industrial cohort, where all individuals have been defined. With such a population at hand, it is natural to think of a case-referent study, where the referents constitute a sample of the population in order to get information about the relative size of the exposed and nonexposed sectors of the population. The dead individuals apparently represent this population as well, i.e. in terms of exposure and nonexposure, and can therefore be taken as referents, unless having died from disorders with a clear relationship to exposure or nonexposure (Axelson, 1979). Also a so-called proportional mortality study could be thought of, but this tends to be less sensitive and conceptually unclear as involving both cases and non-cases in the denominator.

Answer 6

Table XXX may be rearranged as follows and calculations be done according to proposals in the Answer 4, point 7.

Exposure to underground iron mining among cases and referents (non-cancer deaths) aged 50 years and over may be obtained from the death records in the parish of Grängesberg 1966-77 as done below.

Age groups (years)	Cases/ Referents	Exposed	Non-exposed	Total No. of background population
50-65	C	13	3	669
	R	38	66	
> 65	C	20	2	477
	R	145	254	
Total	C	33	5	1146
	R	183	320	
Crude rate ratio, CRR		11.5	(1.0)	
Standardized mortality ratio, SMR		11.5	(1.0)	
Mantel-Haenszel rate ratio point estimate		11.7	(1.0)	
95% confidence interval		5.3-26.0		

252

Note: Since CRR/SMR equals unity, there is no confounding from the age distribution as displayed in the table.

Comment on calculations: The SMR has the character of (observed)/(expected). If no risk is present, the expected number of cases, a*, in each stratum can be calculated. For the first stratum one gets -

$$(a^* \times 66) / (3 \times 38) = 1; \; a^* = 1.73$$

and for the second stratum -

$$(a^* \times 254) / (2 \times 145) = 1; \; a^* = 1.14$$

i.e. the expected is 1.73 + 1.14 = 2.78 versus 13 + 20 observed and the SMR consequently 33/2.87 = 11.5.

The Mantel-Haenszel procedures are well known and the calculations are relatively extensive and therefore omitted. Test-based confidence limits are obtained as shown with regard to questions 7-8 (Miettinen, 1976).

PART 4

Answers 7, 8

Table XXXI refers to matched data, which can be rearranged in a typical display as follows:

Smoking habits in the 28 matched pairs of underground miners

Case	Referent	
	Smoker	Non-smoker
Smoker	17	6
Non-smoker	4	1
Rate ratio	1.5	
95% confidence interval	0.4-5.3	

The rate ratio, RR, is obtained as 6/4 = 1.5 and by the McNemar test one gets $\chi^2=(6-4)^2/(6+4) = 0.4$, i.e. then $\chi=0.632$. Then RR, $\overline{RR} = 1.5^{1 \pm 1.96/0..632} = 0.4;5.3$.

The discordant pairs, here obtained as 6 to 4, were 2 to 1 in ages 50-65 years and 4 to 3 in ages above 65 years.

Answer 9

The numbers involved are quite small and do not permit definite conclusions. However, as mentioned in the introduction, it was indicated that similar small differences had been seen between smoking and non-smoking miners also in other studies. Notice particularly that the confidence interval even goes below unity, i.e. the data per se would even be consistent with a preventive effect from smoking in this sort of mining.

PART 5

Answer 10

From Table XXX one obtains information with regard to the distribution of miners and non-miners in the population as reflected by the referents (not by the cases or the sum of cases and referents).

Hence, for the ages of 50-65 years one gets

$$669 \times 38/(38 + 66) = 244$$

and for ages > 65 years the corresponding calculation becomes

$477 \times 145/(145 + 254) = 173$ or for both age strata
$244 + 173 = 417$

Answer 11

To obtain the excess lung cancers per WLM and 10^6 person-years, one has to calculate the rates for miners and non-miners, simplest by utilizing information from the previous answer.

Hence, the rate R_1 for miners of 50-65 years during the 12 year study period 1966-77 is determined by the 13 cases and the number of person-years at observation

$$R_1 = 13/(244 \times 12) \times 10^6 = 4439.9 \times 10^6$$

and for the nonexposed

$$R_0 = 3/12\ (669 - 244) \times 10^6 = 588.2 \times 10^{-6}$$

The rate difference or excess is consequently

$$R_1 - R_0 = (4439.9 - 588.2) \times 10^{-6} = 3851.7 \times 10^{-6}$$

The exposure is difficult to estimate since only the deceased part of the population is known, which means that the exposure tends to get underestimated. Traditionally one has taken the exposure of the cases as the estimate. The length of exposure was 27 years at about 0.5 WL for the 13 cases. Hence, for eleven months a year (deducting vacation etc.), one gets $27 \times 11 \times 0.5 = 148.5$ WLM and the excess per WLM and 10^6 person-years is $3851.7/148.5 = 25.9$.

The corresponding calculations for the ages of > 65 years, gives 54.3 excess cases per WLM and 10^6 person-years.

Answer 12

Any discussion of the validity (i.e. freedom from systematical errors of bias) of an epidemiological study is somewhat subjective in nature. The authors stressed the following points in the discussion of the study:

- registers were known to be fairly complete;
- migration in and out of the parish should not be differential with regard to exposure and cause of death;
- only non-cancer deaths were included in the matched series in order to obtain a proper reflection of smoking in the mining population. Some distortion is still possible, however, because of (the inclusion of smoking-dependent) cardiovascular deaths among the referents;
- smoking information could be subject to "memory bias" although other experience from Sweden shows that information from relatives is quite reliable (Pershagen and Axelson, 1982).
- slightly longer exposure time for smokers could have meant some uncontrolled (but quantitatively rather unimportant) confounding.

Answer 13

The rather limited size of the study makes all conclusions quite uncertain, except that the Grängesberg miners have had a high lung cancer mortality.

The estimates obtained of the excess lung cancer rate per WLM and 10^6 person-years are in the range of similar calculations for other miners, but the estimate is quite uncertain because it is based on small numbers (for example, taking the 13 cases in ages 50-65 years as a Poisson variate the 95% confidence limits would be 6.92 and 22.23, and hence, the estimate 13.7-44.3, which is quite broad, but still within the range of estimates given in the introduction as obtained from various mining populations).

With regard to smoking, the effect is surprisingly small although the rate ratio has a 95% confidence interval from 0.4 to 5.3, i.e. the information obtained is limited and the study does not even rule out a preventive effect from smoking. On the other hand, a multiplicative effect from smoking and radon daughter exposure seems less likely. In that case, one would have expected an unusually high rate ratio rather than a surprisingly low one and the same would have obtained for the upper confidence bond.

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MORTALITY STUDY TESTING A POSSIBLE ASSOCIATION BETWEEN OCCUPATIONAL EXPOSURE TO FORMALDEHYDE AND CANCER*

Background

Inhalation studies performed in experimental animals have raised the suspicion that exposure to formaldehyde may cause a carcinogenic risk to man. However, a number of epidemiological studies performed in various occupational settings have failed to demonstrate an increased risk of cancer specifically associated with such exposure. At the same time, they could not entirely exclude a possible association, mainly because some of them suffered from flaws such as, lack of data on exposure, multiple exposures, type of analysis (proportional mortality rate), small number of deaths, etc.(Gibson 1983). Therefore, further epidemiological research seemed fully justified.

This study was undertaken in 1982 on request of the management and the union of a plant manufacturing formaldehyde-based resins, after they became aware of the results of experiments. The plant had been active since 1959. The largest production was urea- and melamine- formaldehyde resins. The second largest was synthetic rubbers (styrene) manufactured in a separate department. The potential for exposure to another suspected carcinogen (epichlorohydrin) occurred in the production of epoxy-resins, a small production with very few employees involved.

As usual, designing a study in an occupational setting requires coping with predetermined conditions (characteristics of exposure, number of people, etc.). However, from previous estimates in the United States of America it was known that this was one of the occupational settings with a potential for high exposure at least in the past (Table XXXII).

Table XXXII Concentrations of formaldehyde in occupational environment

Occupational environment	Concentration range		Year
	mg/m^3	ppm	
Fabric cutting and sewing	1.23-13.53	1-11	1955
Dress shop	0.16-0.55	0.13-0.45	1959
Resin manufacture and paper production	19.68-36.9	16-30	1961
Paper conditioning	1.11- 1.97	0.9-1.6	1961
Textile garment production	1.11-3-32	0.9-2.7	1966
Clothing store	1.11-4.06	0.9-3.3	1966
Textile production	0.0-3.3	0.0-2.7	1968
Wood processing	38.38 max	31.2 max	1968
Laminating plants	0.05-13.41	0.04-10.9	1971
Textile processing	smaller than 6.15	smaller than 5.0	1971
Sheepskin dyeing	5.78	4.07-63.41	1971
Funeral home embalming	0.11-6.47	0.09-5.26	1975
Rubber processing	0.49-0.98	0.4-0.8	1975

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* By P.A. Bertazzi, 1984; revised 1985.

From National Institute for Occupational Safety and Health (1976); National Research Council (1980)
Source: International Agency for Research on Cancer (1982), Table 4, p 353.

PART 1

Outcome

Animal studies have pointed out a very specific risk of cancer associated with formaldehyde inhalation, i.e. squamous-cell carcinoma of the nasal cavities.

Question 1.1

Given the experimental results, what type of outcome (cancer) do you consider worth studying?

The cancer experience of workers employed in the plant since 1959 was examined. Information on this type of outcome can be acquired from two main sources: death certificates and hospital (medical) records.

Question 1.2

In principle, which one is preferable? Why is mortality (death certificates) used much more frequently than incidence (hospital records) in the domain of occupational epidemiology?

PART 2

Exposure

Ideally, what one would like to know is the amount of the exposure of each individual subject over time. However, in the realm of non-experimental studies (particularly in occupational settings) the individual exposure can only be approximated.

The data about exposure supplied by the plant were the following:

(a) Type of resins manufactured and amount per year;
(b) Production processes, changes over time, chemicals and raw materials used;
(c) Measurements of environmental exposure (formaldehyde and other chemicals used in the plant), taken at different times between 1974 and 1979 (area samples). Table XXXIII presents typical ambient air concentrations of formaldehyde.
(d) Date of starting and of leaving employment for every worker;
(e) Specific jobs only for current employees; and
(f) Partial reconstruction of the work histories of past employees by interviewing retired workers still living in the area, current workers employed for a long time and foremen.

Table XXXIII Formaldehyde concentration - historical data

Date	No. of samples	Mean value (mg/m^3)	Max. value (mg/m^3)
July 1974	3	3.3	4.3
November 1978	12	1.3	2.5
	12	0.3	0.5
	12	0.6	1.4
December 1978	12	0.2	0.5
January 1979	12	1.5	2.5
	12	0.6	1.0
	12	1.9	3.7
February 1979	12	1.0	1.2
	6	2.7	5.0
	12	2.6	9.8
	4	3.8	6.0
March 1979	12	1.5	3.4
April	12	0.6	1.0
May	12	2.2	5.0

Limit value in Italy: 1.2 mg/m^3 (1.0ppm)

Question 2

Do you consider satisfactory the quality and the amount of information provided by the company? What additional information would you have liked? For any of the above items give reasons for considering it satisfactory or not and make possible suggestions for collecting more detailed and complete information on individual exposure.

PART 3

Population

All workers ever employed in the plant at any time and in any department between 1959 and 1980 for a period of at least six months were considered eligible in the study. The criteria were met by 1332 male and 65 female workers. Their vital status was ascertained as of 31 December 1980 except for a few individuals, as shown in Table XXXIV.

Table XXXIV Follow-up and vital status of workers

	Male	Female
Eligible	1332	65
Traced	1314	65
Alive	1202	61
Dead	112	4
Untraced	18	--

Females were not further considered in the analysis.

Question 3.1

Comment on the above mentioned membership criteria. In particular, is there any good reason for excluding workers with less than six months of exposure?

Question 3.2

Do you agree with the exclusion of female workers?

Question 3.3

Are you happy with the completeness of the tracing?

Part 4

Person years

Workers can enter the plant, and hence the study, at any time within the period of observation. Different times of entry imply different periods of observation (risk) and the contribution of each worker to the total number of person-years (i.e. the amount of population-time accrued by the observed population during the study period) must be calculated.

Table XXXV shows the distribution of the person-years of observation according to attained age and calendar period.

Question 4.1

Examine carefully the distribution of person-years and comment on the possible implications of the distribution with regard to the goal of the study.

Table XXXV Distribution of person-years according to age and study period

Study period	Age (years) 25	25-34	35-44	45-54	55-64	65 and over	Total
1959-1963	302	556	500	306	53	2	1719
1964-1968	736	1428	1162	852	230	6	4414
1969-1973	611	1805	1520	1122	565	47	5670
1974-1978	181	1721	841	1366	818	177	5104
1979-1980	28	517	756	598	382	157	2438
Totals	1858	6027	4779	4244	2048	389	19345

In the analysis stage, person-years of observation are distributed by other relevant variables, e.g. latency, duration of exposure, age of first exposure, etc. Consider the experience of the following workers:

Date of birth: 1 Jan. 1930 - date of employment: 1 Jan. 1960 - date of leaving: 1 Jan. 1973

Let us now consider two variables, namely duration of exposure (5-year categories) and age at first exposure (5-year categories). In the scheme below, the total number of person-years contributed by the workers has been distributed according to two different and alternative methods (A versus B):

Duration of exposure (years)

Method	5	5-10	10-15	15-20	Total
A	5.0	5.0	10.0	0.0	20
B	0.0	0.0	20.0	0.0	20

Age at first exposure (years)

Method	30-35	35-40	40-45	45-50	Total
A	5.0	5.0	5.0	5.0	20
B	20.0	0.0	0.0	0.0	20

Question 4.2

Which one of the alternative methods (A versus B) is correct for duration of exposure and age first exposed? Give reasons for your choice.

PART 5

Results

The following results were obtained regarding selected causes of death in the entire cohort of resins manufacturers (Table XXXVI). For each cause, workers mortality in the period 1959-1980 was compared with two sets of mortality rates:

- Mortality of the national male population of the same birth cohort (5-year categories);
- Mortality of the male population of the same birth cohort (five years) living in the area where the plant is located.

Expected deaths were calculated as usual by multiplying the age and calendar period (five years) specific rates in the referent population by the corresponding number of person-years in the study population. Standardized mortality ratios (SMR) (comparing observed deaths to expected deaths after taking into account age and calendar period) were then calculated as measures of effect. Confidence limits of SMRs were calculated using a program for a desk calculator*, assuming a Poisson distribution of the observed deaths.

Table XXXVI Mortality for selected causes of resins manufacturers
Expected deaths calculated from national mortality rates or local mortality rates

Cause of death	Observed	National Expected	SMR	Confidence Lower	Limits Upper	Local Expected	SMR	Confidence Lower	Limits Upper
All causes	112	103.70	108			121.44	92		
Malignant tumours	42	27.27	154*	111	208	39.72	106		
Alimentary tract	14	8.97	156			13.34	105		
Oesophagus and stomach	7	4.73	148			7.53	93		
Lung	18	7.63	236*	140	373	9.70	186*	110	293
Hematological neoplasm	5	2.49	201			3.25	154		
Cardiovascular disease	24	33.33	72			39.34	61*	39	91
Respiratory disease	6	6.19	97			5.36	112		
Alimentary tract disease	7	11.48	61			12.28	57		
External causes	17	14.66	116			12.23	39		

* Statistically significant (two-tailed p less than 0.05)

Question 5.1

Comment upon the results presented in Table XXXVI and in particular on:
- the number of events which occurred;
- the value of the SMRs for the causes considered.

Question 5.2

Do you agree with the use of several comparison populations? Which are the merits and the possible drawbacks in using local or national mortality as comparison?

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* Such as given by K.J. Rothman & J.D. Boice, Jr. Epidemiologic analysis with a programmable calculator. Program 14. Boston, Epidemiology Resources, 1982, pp 30-31.

Question 5.3

After considering carefully the results in this table, what kind of suggestions would you make to further examine the association under study?

As an additional step towards assessing a possible association between workers' mortality and type of work performed, data were analysed according to a set of variables, on which information was available: age and year of hire, latency, duration of employment in the plant.

Question 5.4

For each variable explain its possible contribution to the study of the association between type of work and cause of death.

In this analysis expected deaths were calculated using local mortality rates. Tables XXXVII, XXXVIII and XXXIX show some results for selected causes. The number and amplitude of the strata for each variable were established within the limits of the study period (1959-1980) a priori, i.e. before knowing the distribution of deaths.

Question 5.5

Do you see any particular pattern or trend for any cause in the Tables XXXVII, XXXVIII and XXXIX? Explain the implication of the findings to the interpretation of the association under study.

The analysis performed so far was aimed at exploring the association between "working in the resins plant" as a possible risk factor in itself and cancer mortality. The suggestion of an increased risk of lung cancer and its apparently weak association with working in the resins plant per se bring us closer to the actual association of interest, i.e. a specific exposure (formaldehyde) and cancer.

Given the available data on exposure, workers were classified according to their jobs (whether they had been working exposed to formaldehyde or not). This was possible because the job mobility in the plant turned out to be rather low: 79% of the workers had been employed in a single job during their working experience in the plant, and almost all workers engaged in the formaldehyde-based resins production did not spend relevant periods of time in other departments. However, detailed work histories were available for only 1088 (82%) of the workers. This problem will be dealt with later. Let us now consider the mortality of workers known to have been exposed to formaldehyde.

Table XXXVII Mortality from selected causes by age at first exposure

Cause of death		Age first exposed (years) 25	25-34	35-44	45 or over	Total
All causes	Obs.	7	18	44	43	112
	Exp.	7.86	17.27	37.52	58.78	121.43
	SMR.	89	104	117	73	92
All cancer	Obs.	2	7	18	15	42
	Exp.	1.43	5.47	14.09	18.74	39.73
	SMR.	140	128	128	80	106
Alimentary tract cancer	Obs.	1	2	5	6	14
	Exp.	0.22	1.24	4.60	7.28	13.34
	SMR.	456	162	109	82	105
Lung cancer	Obs.	1	1	9	7	18
	Exp.	0.02	1.67	3.94	4.07	9.70
	SMR.	5117*	60	229*	172	186*

*Statistically significant (two-tailed p less than 0.05).

Table XXXVIII Mortality from selected causes by latency period

Cause of death		Latency (years) 4	5-9	10-14	15 or over	Total
All causes	Obs.	16	30	34	32	112
	Exp.	22.28	27.51	33.27	38.38	121.44
	SMR.	72	109	102	83	92
All cancer	Obs.	6	11	13	12	42
	Exp.	6.14	9.06	11.65	12.88	39.73
	SMR.	98	121	112	93	106
Alimentary tract cancer	Obs.	2	6	3	3	14
	Exp.	2.03	3.06	3.88	4.36	13.33
	SMR.	98	196	77	69	105
Lung cancer	Obs.	2	4	6	6	18
	Exp.	1.33	2.08	3.00	3.30	9.71
	SMR.	151	192	200	182	186*

* Statistically significant (two-tailed p less than 0.05).

Table XXXIX Mortality from selected causes by duration of exposure

Cause of death		Duration of exposure (years)				Total
		4	5-9	10-14	15 or over	
All causes	Obs.	66	26	16	4	112
	Exp.	67.45	26.51	17.51	10.37	121.84
	SMR.	98	100	91	39	92
All cancer	Obs.	26	11	4	1	42
	Exp.	21.42	8.44	6.13	3.73	39.72
	SMR.	121	130	65	27	106
Alimentary tract cancer	Obs.	7	4	3	-	14
	Exp.	7.08	2.88	2.12	1.26	13.34
	SMR.	99	139	142	-	105
Lung cancer	Obs	11	5	1	1	18
	Exp	5.16	2.04	1.53	0.97	9.70
	SMR	213*	245*	65	103	186*

* Statistically significant (two tailed p less than 0.05)

Table XL represents the results for selected causes of death. Tables XLI and XLII show for the same causes results of analysis according to duration of exposure and latency.

Table XL Mortality for selected causes of workers exposed to formaldehyde (5731 person-years)

Cause of death	Observed	Expected	SMR
All causes	51	46.0	111
Malignant tumours	19	14.9	128
Alimentary tract cancer	8	5.2	155
Lung cancer	5	3.7	136
Hematological neoplasm	3	1.1	273

Table XLI Mortality for selected causes by duration of exposure (workers exposed to formaldehyde only)

Cause of death		Duration of exposure (years) 4	5-9	10-14	15 or over	Total
All causes	Obs.	23	16	9	3	51
	Exp.	22.93	11.79	6.74	4.56	46.02
	SMR.	100	136	134	66	111
All cancer	Obs.	8	8	2	1	19
	Exp.	7.20	3.76	2.32	1.61	14.89
	SMR.	111	213*	86	62	128
Alimentary tract cancer	Obs.	2	4	2	-	8
	Exp.	2.47	1.32	0.83	0.57	5.19
	SMR.	81	304	241	-	155
Lung cancer	Obs.	2	2	-	1	5
	Exp.	1.77	0.92	0.56	0.41	3.66
	SMR.	133	217	-	247	136

*Statistically significant (two tailed p smaller than 0.05)

Table XLII Mortality for selected causes by latency period (workers exposed to formaldehyde only)

Cause of death		Latency (years) 4	5-9	10-14	15 or over	Total
All causes	Obs.	4	14	15	17	50
	Exp.	7.27	9.49	11.08	18.17	46.01
	SMR.	69	148	135	94	109
All cancer	Obs.	3	5	5	6	19
	Exp.	2.05	2.98	3.83	6.03	14.89
	SMR.	146	168	131	100	128
Alimentary tract cancer	Obs.	1	4	1	2	8
	Exp.	0.70	1.07	1.36	2.05	5.18
	SMR.	144	376*	74	97	155
Lung cancer	Obs.	1	1	1	2	5
	Exp.	0.49	0.65	0.97	1.55	3.66
	SMR.	203	154	103	129	136

*Statistically significant (two-tailed p smaller than 0.05)

Question 5.6

Is there any suggestion of an association between exposure to formaldehyde and mortality for the causes considered?

Question 5.7

Which are the major possible biases in this analysis?

Question 5.8

Would you suggest any further analysis?

Giving the above mentioned drawbacks in the comparison of an occupational cohort with the general population (either national or local), it was decided to perform an internal comparison between workers exposed to formaldehyde and workers without such exposure. Three subcohorts were thus identified: exposed to formaldehyde, never exposed to formaldehyde, unknown exposure (workers without detailed work history).

Table XLIII presents results for selected causes in the subcohorts. Also the number of person-years in each subcohort is reported. Clearly, workers with "unknown" exposure experienced the least favorable mortality: the excess for all cancers and lung cancer is statistically significant. Workers with "other" exposure (i.e. no formaldehyde) exhibited a mortality lower than expected except for the one caused by lung cancer.

Table XLIII Cancer mortality by type of exposure in the plant

Cause of death		Type of exposure (person-years)		
		Formaldehyde (5731)	Other (10527)	Unknown (4078)
All cancers	Obs.	19	9	14
	Exp.	14.9	16.7	8
	SMR.	128	54	174*
Alimentary tract cancer	Obs.	8	1	5
	Exp.	5.2	5.5	2.7
	SMR.	155	18	187
Lung cancer	Obs.	5	6	7
	Exp.	3.7	4.1	1.9
	SMR.	136	148	358*
Hematological neoplasms	Obs.	3	1	1
	Exp.	1.1	1.5	0.7
	SMR.	273	67	143

* Statistically significant.

There were no ways, at least for the moment, to ascertain the "unknown" exposure. A very simple attempt was made in order to estimate the possible bias introduced in the results by the lack of information about a certain proportion of working histories. Thus, workers with unknown exposure were alternatively assigned either to the subcohort of formaldehyde exposed workers or to the subcohort of workers with other exposure. The results turned out to be as illustrated in Table XLIV.

Table XLIV Results of the analysis with the assignment of workers with unknown exposure alternatively to the group of formaldehyde exposed or other exposure

Cause of death		Type of exposure (person-years) Formaldehyde (5731)	Formaldehyde + unknown (9809)	Other (10527)	Other and unknown (14605)
All cancers	Obs.	19	33	9	23
	Exp.	14.9	22.9	16.7	24.7
	SMR.	128	144	54	93
Alimentary tract ca.	Obs.	8	13	1	6
	Exp.	5.2	7.8	5.5	8.1
	SMR.	155	166	18	74
Lung cancer	Obs.	5	12	6	13
	Exp.	3.7	5.6	4.1	6
	SMR.	136	214	148	216
Hematological neoplasms	Obs.	3	4	1	2
	Exp.	1.1	1.8	1.5	2.2
	SMR.	273	222	67	92

Question 5.9

Consider the results and comment on their relevance for the evaluation of the association under study."

PART 6
Discussion and findings interpretation

To summarize the findings, a certain association between exposure in the plant and cancer mortality of the employees is in the data. However, as already noted, there was no consistency throughout the different steps of the analysis and many limitations affected the study. A thorough discussion is warranted.

When an association between an exposure and an outcome is in the data it does not necessarily mean that it is causal. Alternative explanations exist, i.e. chance and bias. Let us consider these possible explanations first, focussing on cancer mortality.

Question 6.1

Consider results regarding all cancer, lung cancer, alimentary tract cancer and hematological neoplasms. Can any of the excesses be explained by chance alone?

A systematic error (bias) can be the actual explanation of an observed association. This point has been partially addressed also in previous paragraphs. There are three common sources of bias:

- confounding (e.g. alcohol may appear associated with lung cancer not because it is a true risk factor, but only for its association with cigarette smoking, the true risk factor);
- selection of subjects entering in the study; and
- information available.

Question 6.2

Discuss each of the above sources of bias in the view of interpreting results regarding cancer mortality.

At this stage, after discussing "chance" and "bias" it is a suitable opportunity to consider "causality" as an explanation of the findings. This discussion implies the consideration to be given to a set of criteria which can help us in a "non-experimental" setting: the selected animals (patients) are not treated with a known dose (treatment), yet the existing data must be exploited to mimic as closely as possible this very situation. The following are some of the criteria to be followed in order to evaluate the causal nature of an "exposure-outcome" association and strengthen the interpretation of the study results: strength of the association, dose-response relationship, specificity of the association, and consistency of results.

Question 6.2

Discuss each of the listed criteria of "causality" in the context of results yielded by the study.

Question 6.4

Are there other criteria useful to this goal?

Question 6.5

Would you call this study "negative"?

INSTRUCTOR'S NOTES
FORMALDEHYDE AND CANCER

Purposes of the example

The main objective is to illustrate whether and how an association between exposure and disease can be looked at in a typically non-experimental situation, i.e. an industrial cohort examined retrospectively (historically).

The focus is here on what can be done, given the existing information and what cannot be inferred given the limitations inherent in studies of this type. This example on formaldehyde exposure has been chosen for its current relevance and interest. Experimental data and previous human studies exist but they are inconclusive as to the carcinogenic risk to humans (Gibson, 1983). This study seemed also typical of the problems and limitations encountered when conducting similar studies.

Specific purposes

Design, study conduction and analysis	- Outcomes to be considered; - How to exploit existing information on exposure; - Admission criteria into the cohort; - Suitability of referent populations; - Guidelines for subcohort analysis;
Result interpretation	- Need to explore all possible explanations for the findings: chance, bias, causality; - Short discussion on "negative" studies.

PART 1
Outcome

Answer 1.1

Although the experimental studies pointed out a very specific risk of cancer, it is essential to consider the full range of cancers when studying a human population. This is due to the fact that, with a very few exceptions, chemical carcinogens are multipotential. In addition, the sites at risk are not necessarily the same in human beings as in experimental animals. It is also worth mentioning that, given the rarity of sinonasal cancer, in order to uncover such a risk, a very large population would have been required.

271

Answer 1.2

The information on cancer type and sites is, in general, much more accurate on hospital records than on death certificates, since the full medical diagnosis is not always reported on death certificates. Therefore, in principle one would prefer to study incidence rather than mortality.

However, since an occupational cohort is usually composed of people living in different areas who have been moving over time etc., cancer incidence can be successfully investigated provided that:
- a cancer registration system exists; and
- such system is nation- or regionwide.

Moreover, since the study covers a historical experience, the system should be in existence for a sufficient period of time (the period relevant for the study of the association of interest). Such sufficiently old and functioning registers exist only in a limited number of countries. Causes of deaths, instead, have been routinely recorded for a fairly long time in almost every country. Apart from confidentiality aspects imposing problems in some countries, they are available on an individual basis for scientific purposes. Moreover, studies performed in different countries have demonstrated that, at least for the main type of cancer, there is a satisfactory correspondence between clinical or pathological diagnosis and death certification (Alderson & Medde, 1967, de Faire, et al. 1976; Percy, et al. 1981, Gobbato, et al. 1982). This is also due to the fact that, typically, the case fatality rate for cancer is high (i.e. the time between diagnosis and death is rather short).

Considering all the above, the easier accessibility of death records make mortality the most widely used outcome measure in occupational cohort studies. For these same practical reasons (including the lack of a cancer registration system), this study was designed as a mortality study.

PART 2

Exposure

The main features of exposure we have to consider are type, level and duration.

Type

The exposure may be single or mixed. In the working environment, like the one being studied, exposure is often mixed and changing over time. In the plant under consideration changes can occur in:
- individual production processes,
- basic compounds and raw materials involved; or
- type of airborne chemicals.

So the information about the type of exposure may be considered as sufficiently good. It is also necessary to know the chemical and physical characteristics of the substances, because they can determine the route of absorption.

Level

Estimates of the level of exposure could be obtained from different sources:

- The amount of chemicals involved in different production processes over time;

- Environmental monitoring (measurements of the concentration of the substances in environmental air with the use of area or personal sampling). The use of personal sampling normally allows a more global evaluation of the exposure, since it takes into account, for instance, workers displacements during the workshift and the variation of concentrations in different areas. The environmental data available in the study were, instead, fixed measurements giving some general information about the exposure. It can be seen from Table XXXIII that many measurements were above the current limit value. Yet, the job-specific exposure for individual workers cannot be evaluated. It is important to underline that in many occupational studies it is difficult to reconstruct the single subject exposure accurately (for instance, none of the studies published so far regarding occupational exposure to formaldehyde and cancer was able to provide detailed information on exposure) (Gibson, 1983);

- A third possible source is biological monitoring (Lauwerys, 1983) which gives the most exhaustive information on the actual exposure of individual subjects. However, biological monitoring is currently available for a limited number of chemical compounds. Theoretically, biological monitoring of formaldehyde exposure is possible (e.g. formic acid in urine) but there are no sound and valid methods available for large populations. In any case, no biological measurements had been performed in this plant.

Duration

It is necessary to know since when and for how long the workers have been exposed. The information to be collected includes not only the number of years or months in which the subject has been exposed, but also the period of time, since changes in production processes may have modified the exposure level. In this study the examination of plant records allowed the identification of the date of beginning and of leaving employment for each worker. The reconstruction of individual work histories was carried out by interview. This method can be used when detailed recorded work histories are lacking.

Other limitations might be discussed, including:

- Information may be more accurate for subjects hired recently than for those hired in the past;
- It is not easy to reconstruct the work histories of the individuals employed for a short time; and
- Information about a subject may be doubtful when interviewing workmates on jobs held by former employees.

PART 3
Population
Answer 3.1

It is important to consider for inclusion into the study all workers employed from the beginning of the production of interest and to perform some kind of checking of the completeness of the list provided. Workers with very recent exposure might be less interesting for the association under study: however, they can be easily separated in the analysis stage and may become of greater interest for a further follow-up. There are no sound scientific reasons for excluding workers with less than, say, six (or four or twelve) months of exposure. However, workers with a rather long period of exposure are relevant for the study of the exposure-outcome association of interest. On the other hand, practical considerations suggest that workers with a very short exposure in the plant may have had several other different kinds of exposure. In countries where the follow-up must be conducted on an individual basis, these workers usually turn out to be the most difficult to trace, since they tend to move frequently. This is a practical reason for not including them in the follow-up. Moreover, such workers are also different, since in general they experience higher morbidity and mortality (Gilbert, 1982).

Answer 3.2

The restriction of the study to male workers simply means that the results may not be applicable to female workers, since sex could in some way affect the association examined. The exclusion of female workers from the analysis, however, rested essentially on their total number (65). At any rate, these are the characteristics of the four cases of death observed among female workers:

Case/Cause of of death (years)	Age of death (years)	Latency (years)	Duration of exposure (years)	Age at hiring	Year of hiring
1 Bladder cancer	58	19	6	39	1961
2 Malignant lymphoma	33	1	1	32	1962
3 Liver failure	43	8	1	35	1964
4 Unknown	25	10	6	15	1963

Answer 3.3

Vital status was ascertained for 98.6% (1314/1332) of the male workers, a rather high proportion. The point of interest is, however, the one of selection. Did the untraced people have some peculiar characteristics in common? Although, sometimes, one can try to obtain some information on the untraced, in general untraced people remain unknown. Therefore, one tries to trace the study population as comprehensively as possible just to avoid selection problems.

As a rule of thumb, a proportion of 95% or more is considered to protect a study from major selection bias. A conservative approach to this issue is to consider all unknown people as alive at the end of the follow-up in the analysis stage. On the other hand, a conservative view is not necessarily the best standpoint. One could, for instance, choose an opposite view and consider all untraced workers as dead at the end of the study or at the date of their loss to follow up. Between these extreme options, others exist, as for instance, attributing lost people to the dead or alive category according to the same proportional distribution observed among the traced ones.

PART 4
Person-years

A more detailed description of person-years calculation can be found in the exercise regarding vinyl chloride and cancer. The illustration of the underlying concept and calculation of an example by the instructor is recommended here.

Answer 4.1

With regard to the present example, one can note that only 1719 person-years (8.9%) have been at risk before 1963. Therefore the large majority of the cohort will have a latency period of less than 20 years. Furthermore, only 389 person-years (2.0%) are in the age categories of over 65 years. Two problems arise:

a) The age structure of this rather young population makes it less likely that any excess of cases should appear, since effects usually are seen later in life;

b) Given the long latency period required for the study outcome (death) to occur, the chances of observing it are diminished even in the case that exposure did cause harmful effects i.e., this view is supplementary to what has already been said above.

A longer period of follow-up seems to be required in order to examine the associations under study.

Answer 4.2
Duration of exposure

Method A is correct with variables like latency, cumulative exposure, etc. Person-years must be assigned to the category of duration of exposure attained by the subject during the period of observation. Thus, although the overall duration of exposure of this subject is 13 years, his person-years contribution must not be attributed to the category 10-15 years, but stratified as shown. Person-years are accumulated over time, therefore person-years of the first five years of exposure must be assigned to the correspondent category. Person-years will be assigned to the next category only after this period has elapsed, etc.

In addition, note that the length of exposure is 13 years, but his person-years contribution is 20 person-years since the period at risk for a subject does not end with the end of the exposure but continues until the study closes or the subject dies (whichever comes first). All person-years, after cessation of exposure, will be assigned to the last category of duration of exposure (so, there were ten person-years in the category 10-15 years).

With method B a uniform duration of exposure would have been assigned to the subject, which is less appropriate, because the full degree of exposure has not yet been achieved in the beginning of the follow-up of this individual.

Alternative approaches exist however, i.e. the material might be divided into subcohorts with regard to the finally obtained duration of exposure.

Age first exposed

Method B is correct here. In fact, age at first exposure does not change over time. The worker's experience is related to that particular age at the beginning of exposure. Method A would be correct when considering attained age.

In summary, method A is suitable for variables whose values change over time; method B for variables constant over time (e.g. sex, race, etc). A good example of this issue can be found in Wagoner and coworkers (1976).

PART 5

Results

Answer 5.1

The total number of deaths observed (112) is small compared with the size of the cohort. This was actually to be expected, given the age structure of the study population (see above). For some causes the number of deaths is very small: this suggests caution in interpreting the values of specific SMRs (e.g. leukemias).

SMRs for some causes of death are above 1.00, some below, some are statistically significant, some are not.

Overall mortality. There is no significant difference between observed and expected deaths. The SMR values, however, are somewhat higher than usually obtained when comparing a cohort of workers with the general population. This result calls for a careful examination of the individual causes of death.

Cancer. SMRs are in general high but have different values according to the sites involved and the comparison population considered. The SMR for all cancer is statistically significantly raised only in comparison with the national mortality. Cancers of the alimentary tract were increased (although not significantly) but only compared with national mortality. Lung cancer seems to be consistently elevated with both comparison populations; the elevated SMRs are statistically significant. The consistently raised SMR values for hematological neoplasms are, instead, not significant. Cancer mortality, therefore, seems to warrant further analysis.

Cardiovascular disease. Observed deaths are clearly below expectations. This indicates that, as far as these causes are concerned, the study population underwent some selection phenomenon in comparison with the general population, an example of "the healthy worker effect."

Respiratory disease. No similar selection factors seemed to have acted with regard to these causes of death, contrary to what is usually found in similar studies. One possible explanation is that the working environment itself represented a risk factor for respiratory diseases.

Alimentary tract disease. The observed deaths are well below expectations contrary to what was observed for malignancies of this same site.

Accidents. There is a slight but not significant excess of deaths in comparison with both referent populations, which was not accounted for by work accidents.

Answer 5.2

The point of interest is not the number of the comparison populations but their suitability. A suitable comparison population would be one with the same mortality experience as the population under study in absence of the exposures examined. In other words, another working population with a comparable distribution of general risk factors for mortality (age, sex, socioeconomic class, lifestyle-factors such as smoking, other selection factors for survival). Moreover, also the type and quality of the information must be comparable in the population contrasted (validity of information). Unfortunately, in occupational mortality studies, such a comparison population is very seldom available. Hence, in general, a geographically defined population - for which mortality statistics are routinely collected in the majority of the countries - is selected for comparison. However, an occupational cohort is composed by people who underwent many selection processes (both natural and artificial like pre-employment fitness examination) and therefore are selected as regards health status, and, hence, risk of death. This introduces a bias in the comparison, often referred to as "healthy worker effect" (Fox & Collier, 1976; McMichael, 1976). (Note in Table XXXVI, cardiovascular disease and alimentary tract disease).

The use of a local population instead of the national one is indicated in countries where there are regional differences in the risk of mortality for the causes of interest (as was the case in this study). In this way one tries to control, at least implicitly, for a number of sociocultural risk factors. For a further and thorough discussion of this issue, see "Expected numbers in cohort studies" published by the MRC Environmental Epidemiology Unit in England (1984).

As far as the validity of information is concerned, the source from which causes of death were ascertained was exactly the same for the workers and the general population.

It can be seen from the Table XXXVI, that cancer mortality was rather high in the region where the factory was located and consequently the number of expected deaths were larger when using local rates rather than national mortality rates.

Answer 5.3
Possible suggestions are the following:

- further in-depth analysis of cancer death (especially lung cancer);
- take into account other variables relevant for the examination of the association under study (e.g. smoking, latency, age, period, etc.); and
- classify workers according to the specific type of exposure.

Answer 5.4
Age of hiring. When considering certain types of disease, particularly cancer, there is a different susceptibility to possible risk factors at different age. In addition, a late age of hiring implies previous unknown exposure.

Years of employment. Exposure to the same agent in different calendar periods may produce quite different risks depending, for instance, on the hygienic conditions of the plant, the type of production process, the concomitant exposures, the technological changes and so on.

Latency. As a general model, for occupational cancer the time-span between the beginning of exposure and the occurrence of the disease (death) is rather long (often decades). There are only few exceptions (e.g. some leukemias). What is called latency represents a rough estimate of the "induction period" of the diseases and of the "latent period" of their signs and symptoms to appear.

Duration of exposure. When no accurate individual quantitative measurements are available - as usual in this kind of investigations - one can try to approximate a dose/response relationship using the duration of exposure as "dose" indicator under the assumption that the longer the duration of exposure, the higher the risk.

Answer 5.5
Table XXXVII. No definite trends or particular patterns are appreciable for all causes and all malignancies. There is some suggestion of a negative trend for digestive cancer; the over fourfold excess of the less than 25 category is based on one death only. Overall, for the above causes, the older the age of hiring, the lower the risk: this can imply some particular kind of selection for these workers or the simple fact that the background risk increases with age. Hence, the rate difference would perhaps be a better measure than the risk ratio. Lung cancer deaths are more than twice as high as expected in the 35-44-year category. The excess of the 25-year category is based on too small numbers to be meaningful.

Table XXXVIII. No definite trends or patterns obtained. Lung cancer deaths are higher than expected in each category. No statistically significant observed/expected ratios were obtained.

Table XXXIX. Given the length of the study period (22 years), very few people had more than 15 years of exposure, hence very few deaths have been observed in this category. Two points seem to be of special interest. One is the significant mortality deficit for the workers with the longest exposure. These could simply be another reflection of the selection phenomenon previously discussed. Workers not only undergo selection when entering the industry but also during their working experience: those who develop some health impairment leave the industry or the job; they remain in the study, but their duration of exposure remains rather low. The second point deals with lung cancer. The SMRs are significantly increased in the categories with the shortest exposure. Remember, however, that few people had a longer experience. On the other hand, similar findings - if confirmed after a longer follow up - are opposite to the assumption made above (duration/risk relationship).

Overall, these findings point out, again, an excess risk of lung cancer without, however, giving definite clues to a sound interpretation of the association between work experience and lung cancer deaths. There is a strong, further indication for continuing the study in time. One possibility left, considering the available data, is an analysis by specific type of exposure.

Answer 5.6

All SMRs are increased, but none of them is statistically significant. Hematological neoplasms are few, but clearly in excess. There is some suggestion of a mortality experience (overall and for specific causes) higher among formaldehyde-exposed workers as compared to the local population. In particular, the SMR for lung cancer is not statistically significant. There are no clear-cut patterns or trends of mortality by duration of exposure. The number of deaths is rather small in several strata. The greatest risk affected, seemingly, workers with five to nine years exposure: the SMR for all cancers is significantly increased in this category. Analysis by latency yielded higher SMR values for workers in the less than ten years categories. Note here also the small number of deaths in several strata. For digestive cancer, a statistically significantly increased SMR was obtained in the 5-9-year category. No sound association is apparent from this analysis.

Answer 5.7

Misclassification of exposure due to lack of detailed work histories for all workers (18% missing).

Answer 5.8

An internal comparison between workers exposed and not exposed to formaldehyde may be of some help.

Answer 5.9

All cancer. If we assign all "unknown" to "formaldehyde exposed" the SMR changes very little and increases a little more above 100. Under the opposite assumption the SMR among "other" clearly increases but remain below 100. This means that even if it is assumed that all workers with unknown exposure (whose cancer mortality was significantly raised) were not exposed to formaldehyde, still the excess observed in the whole cohort seems to be confined to

279

formaldehyde exposed. Similar considerations apply to alimentary tract cancer and hematological neoplasms. A similar pattern could have been anticipated given the large difference of the SMRs values for "formaldehyde exposed" and "other".

For lung cancer, the background SMR values for "formaldehyde exposed" and "other" are similar. Therefore, the excess mortality falls in either category depending on to which one workers with unknown exposure are assigned. It follows that without knowing the detailed work histories of each workers there are no grounds for attributing to formaldehyde a specific role in determining the observed excess of lung cancer.

The assumptions made are the most extreme. Another way to handle this problem is to assign "unknown" (person-years and deaths) to each category of known exposure according to some criteria of proportionality, weighting, etc.

PART 6

Discussion and findings interpretation

Answer 6.1

It might be worth recalling briefly what is meant by "chance" in this domain.

When several samples are drawn from the same population, different results are usually obtained. As a consequence, differences, say, between exposed and nonexposed may indicate, either that the two groups belong to different populations, or that they differ only by chance, being usually different samples taken from the same population. To rule out chance as an explanation, usually a null hypothesis (H_0: the groups are drawn from the same population, or SMR = 100) is tested and the results are expressed by the "p value", i.e. the probability of obtaining a result like the one of the study or a more extreme one, given that H_0 is true. If this probability is less than a prefixed value (say 0.05) an alternative hypothesis should be considered (H_A: the groups are drawn from different populations or the SMR differs from 100).

It should, however, be stressed that statistical significance does not in itself provide any proof of causality. Moreover, when the findings of a study are statistically significant it does not necessarily follow that they are relevant or even meaningful. Statistical significance is also considerably affected by sample size. A large sample is very sensitive to small deviations from the null hypothesis, whereas a small sample is sensitive only to larger deviations. As the sample size is increased, biologically unimportant differences might turn out to be statistically significant. Therefore, especially in studies which involve large groups of people, the magnitude of the effect is much more important than its statistical significance.

Note: It is advisable to calculate lower and upper confidence limits of the risk estimate (SMR) and not only the "p-value". Confidence intervals, in fact, convey information on both magnitude and precision of the effect estimate. The larger the interval, the less precise is the estimate. When 1.00 is not included in the interval the result is statistically significant at the chosen level.

In the whole cohort, excess mortality for lung cancer clearly cannot be explained by chance alone. However, other increased SMRs (e.g. hematological neoplasms) cannot be dismissed on the sole ground of their being statistically not significant: they warrant further analysis. The same consideration applies to results within subcohorts: thus, for instance, in a particular latency category (5-9 years) the excess of alimentary tract cancer becomes significant.

On the other hand, the statistically significant SMRs do not prove that the association is causal. Other factors must be taken into account.

Answer 6.2

Here again it might be necessary to expand on what is meant by confounding, etc. (Kleinbaum, et al. 1982). As regards the example, the following are the points of main interest:

Confounding: is there any risk factor alternative to the exposure examined capable of explaining the excess mortality noted? At least two candidates exist: tobacco smoking and other exposures. Information on smoking was not available in the study and thus there is the possibility of a systematic difference in smoking habits in the populations compared. Smoking was particularly important since respiratory organs were the sites most probably at risk. The only attempt made to control this possible bias was to use for comparison a local population, whose smoking habits may be assumed less different than those of the national population from the smoking habits of the study cohort. And in fact the SMR for lung cancer decreased with the use of the local population but the value remained significantly elevated. The lack of this kind of information certainly limits an exhaustive interpretation of the findings. Recall, however, that an SMR of more than 2.00 to 2.50 is unlikely to be totally explained by smoking habit differences (Axelson, 1978).

As regards other exposures, this possible confounding factor has been controlled by carefully considering all the exposures existing in the plant over time.

The mentioned exposure to epichlorohydrin (brief in time, with limited production) or styrene did not appear as a possible confounder. The types of solvents used are not known to be associated with hematological neoplasms. No control was, indeed, possible for previous occupational exposure and for non-occupational exposures (leisure activity, etc). In the subcohort analysis by type of exposure, confounding due to smoking was the least likely given the uniform socioeconomic and educational level of the groups examined.

281

Selection: all workers, active or retired, were included in the study. Thus, no selection phenomenon due to "missing workers" could be advocated. The follow-up, on the other hand, was almost complete. There was, instead, a selection phenomenon in the comparison of workers with the general population (healthy worker effect). From what is known, this selection phenomenon biases the risk estimate in the cohort towards the null. This is, however, not necessarily true for every cause. In any case, the magnitude of the bias is not known.

Information: the major problem was the missing detailed work history for 18 % of the workers. Another problem was the way work histories were collected, i. e. mainly by interviews and not by extracting records. If the type of misclassification (differential/non-differential) was known, the direction of the bias could be discussed, which in the case of non-differential misclassification is always towards the null. An information bias cannot be ruled out as possible explanation of the findings for specific type of exposure. The analysis presented in Table XLIV did not clarify this misclassification problem at least for lung cancer.

Answer 6.3

For full discussion see, among others, Susser, 1973 and Hill, 1984.

Strength of the association: the higher the relative risk the stronger the association. When the value of the RR estimate (e.g. SMR), and especially its lower confidence limit, is well above 1.00 it is unlikely, as previously discussed, that chance will be a sufficient explanation and that a confounding factor strong enough to explain the large excess risk has passed completely undetected. In this study there was a strong association between having worked in the factory and lung cancer mortality. When considering the specific type of exposure, the strongest associations were among "unknown"; for workers exposed to formaldehyde the SMRs did not indicate a very strong association, with the possible exception of hematological neoplasms: however, the lower confidence limit for these cause of death was below 1.00.

Dose-response relationship: the doses are unknown. In similar cases the "dose" can be approximated by using "duration of exposure". A clear dose-response relationship between the duration of exposure and the mortality did not appear either in the whole cohort or in the formaldehyde exposed workers.

Specificity of the association: if the association is limited to a specific type of exposure or to a specific type of disease, then there is a strong argument in favor of causality. (Consider, however, that a single exposure may cause different effects and a single disease have more than one "cause"). A very specific outcome could have been expected in this study: sinonasal carcinoma, however none occurred. Lung cancer is a rather specific entity, but there can be important hystological differences. Alimentary tract cancer is a rather broad category of cancer, as are hematological neoplasms.

On the other hand the highest SMRs were related to a rather broad exposure type, i.e. working in that factory. Analysis by specific exposures suggested that the cancer risk was mainly confined to workers holding a job encompassing exposure to formaldehyde. However, this was not demonstrated for lung cancer (for the reasons already discussed) and the values of SMRs did not indicate a strong association.

Consistency: External - no previous epidemiological studies showed an excess of lung cancer in human beings occupationally exposed to formaldehyde. There is preliminary evidence from the other epidemiological studies of a possible excess of digestive cancer and hematological neoplasms among workers with a similar exposure.

Internal - the excess mortality from different cancers does not seem completely consistent throughout the different steps of the analysis: consider, in particular, the lack of a trend according to latency period and the scanty pattern according to age first exposed and duration of exposure.

Answer 6.4

Other useful criteria are: temporal aspect of the association; biological plausibility; intervention study.

- In this particular study there is no doubt that the effect comes after the exposure (in cross-sectional study this is not always the case). As already noted, however, the latency assumption has not been fully satisfied.
- Biological plausibility calls for consideration of the current biological and experimental knowledge in support of the observed association. The respiratory tract can certainly be considered "biologically" at risk. Less at hand is the explanation of a possible risk for digestive organs and lymphatic and hemopoetic tissues.
- Probably the most convincing evidence for a causal relationship is found in an intervention study where a change in the exposure results in a change in the risk. No such evaluation was available for this plant.

Answer 6.5

A "negative" study is not one yielding no clearly positive results but one yielding clearly negative results. The difference must be appreciated (Hernberg, 1981).

The discussion should be recalled about statistical significance and the cancer results for formaldehyde exposed workers considered. None of the SMRs was statistically significant (Table XL). Can it then infer that there is no excess of cancer risk? Consider the table below.

	Obs.	Exp.	Power (1- beta)	Minimum significant RR detectable
Alimentary tract cancer	8	5.2	.80	2.46
Lung cancer	5	3.7	.80	2.90
Hematological neoplasms	3	1.1	.80	5.36

Given the size of the study population (person-yrs) and an alpha 0.05, the study had a good power (0.80) of detecting only SMRs of 2.46 or more for digestive cancer, 2.90 or more for lung cancer, 5.36 or more for hematological neoplasms. This means that the actual risk noted among formaldehyde exposed workers (see SMRs value) were too low to be successfully detected as statistically significant by this study (given a power of 0.80 and alpha = 0.05).

It can than be concluded that the study was "inconclusive" from the statistical point of view, which is very far from saying that it was "negative". A continuation of the follow-up with an increase in number of person-years and deaths could make the study capable of detecting as significant risks as "low" as the ones currently observed.

If instead, the results for lung cancer in the whole cohort versus local population (SMR = 186) are considered, calculations would show that the study had a power of nearly 0.80 to detect it. This provides evidence, that this result is probably "positive".

Calculations were based on formula reported in Haines and Shannon (1983). Simpler formula for approximative calculations are given in Beaumont and Breslow (1981).

- A true negative study must also be "sensitive" (informative). Consider first latency. In general similar studies become informative after 20 years of latency: the maximum latency period allowed by the study was 22 years. Thus, most probably, the most likely time of occurrence of deaths was not examined. Also exposure categorization was "insensitive": accurate levels of exposure were not available and few person-years experienced exposure longer than 15 years.

In summary, the study could not demonstrate an association between formaldehyde exposure and cancer risk. However, this association could not be ruled out. The major limitations were size of the cohort (number of workers and period of follow-up) and quantitative information on specific exposures. The lung cancer risk noted in this plant needs further study (including consideration of smoking habits). The cancer risks to formaldehyde workers can neither be dismissed nor considered proved. A longer follow-up would be most useful, along with a further attempt to document individual work histories. The consistency of these results with preliminary findings in other studies should also be stressed.

Finally, it might be worth summarizing the logical path followed in this study. At a first glance, the cancer mortality of the cohort of resin manufacturers with a potential for exposure to formaldehyde appeared remarkably increased; the data were further analysed in a stepwise progression, all the relevant factors taken into account (admittedly with the limited information available) and alternative explanations for the findings considered. The results turned out to be less exciting (only for the investigators), but the piece of information added to the scientific knowledge regarding formaldehyde and cancer was, in this way, more credible.

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EXPOSURE-RESPONSE RELATIONSHIP BETWEEN STYRENE EXPOSURE AND CENTRAL NERVOUS FUNCTIONS*

Introduction

In the early 1970s little was known about the neurotoxic effects of styrene exposure. There were some reports on electroencephalographic (EEG) changes, one on reduced conduction velocities in peripheral nerves, and a few case reports on intoxicated workers suggesting central nervous system (CNS) effects. Some studies also suggested that styrene had a short-term effect, e.g., prolongation of the reaction time, but in general the literature was scanty indeed and the scientific basis for the USA threshold limit value (TLV) of 100 ppm - used in many other countries as well - was very weak.

Because the use of styrene had increased sharply in the reinforced polyester plastic product industry in Finland, the Finnish Institute of Occupational Health in 1973 decided to initiate a broad epidemiological survey, aiming at:

1) developing a biological monitoring test;
2) studying the neurotoxic effects of longstanding styrene exposure; and
3) providing exposure-response data to serve as a basis for a hygienic standard.

The present study will focus on the third purpose, and only a short summary of the other findings will be given here.

PART 1

Selection of exposure variable

The first step of the study was to scrutinize the correlation between the concentration of mandelic acid, a metabolite of styrene, in urine, and the 8-hour time-weighted average (TWA) concentration of styrene in workroom air. Styrene in ambient air was measured during an entire normal workday (except for Monday) and time-weighted to 8 h. It was analysed by gas chromatography (Engström, et al. 1976). Urine was sampled at the beginning of the work day, 4 h later, and at the end of the workday and thereafter 4,8 and 15 h after termination of exposure. The sample taken at the end of the workshift was used for the correlation study.

A highly significant correlation was found ($r = 0.87$, $p < 0.001$). Fig. 8 shows the correlation. It can be seen that the USA TLV of 100 ppm, recommended in 1973, corresponded to an average postshift mandelic acid concentration of about 2200 mg/l urine (95% tolerance limits approximately 1000 - 4500 mg/l). It can be added that the gas chromatographic method used for the determination of mandelic acid is specific in contrast to some older methods (Engström, et al. 1976). Hence there is no "background", i.e., no mandelic acid is found from the urine of nonexposed subjects. Therefore a reference group was not needed in this exercise.

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* By Sven Hernberg & Hannu Härkönen, 1984; revised 1985.

288

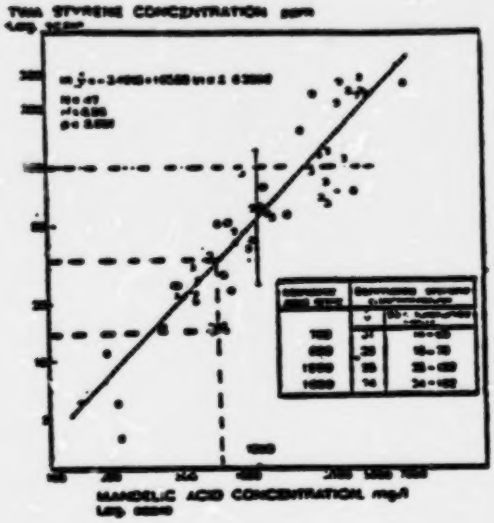

Fig. 8. Correlation between the 8-h (TWA) of styrene exposure and urinary mandelic acid concentration, adjusted to a constant specific gravity of 1.018.

Question 1

How do you interpret these figures? Which value of urinary mandelic acid concentration would you select as a "safe" value from the point of view of not exceeding the TLV exposure?

PART 2

Qualitative aspects

The next phase of the study was a cross-sectional medical examination of laminating workers. Altogether 98 male workers (median age 28 years, range 16 to 54 years, median exposure time 5.1 years, range 0.5 to 14 years) working in 24 factories were examined clinically, neurophysiologically and psychologically. The laminating industry in Finland comprises mainly small factories with a few employees only. Most of the exposed workers are male. These considerations led to exclusion of female workers from the study group.

Practical difficulties in organizing a thorough clinical examination, requiring among other things urine sampling during five weeks, travel and one day's stay at the Institute of Occupational Health, for a group of workers employed by small factories scattered all over the country, restricted the size of the group available for study. Hence, the sample size of 98 was not derived from any power calculations, but merely a result of practical aspects. This is a very common situation in epidemiology, where one often has to utilize what is available rather than consider optimal sample sizes from a statistical point of view.

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The workers' symptoms, both general and those thought to be typical of solvent exposure, were ascertained by means of a self-administered questionnaire comprising 33 questions. A clinical examination was given each subject, and the neurophysiological examinations comprised an EEG examination (two subjects had no EEG-recording) and nerve conduction velocity measurements for those 40 subjects who reported most subjective symptoms (their exposure levels were not known at this stage). Finally, a comprehensive psychological test battery, comprising tests for a wide variety of mental functions, was given all subjects. The test battery was composed of intelligence tests, which are all subtasks from the Wechster Adult Intelligence Scale (WAIS), memory tests, including three verbal and one visual test, tests for visual perception and motor performance, which require coordination and which measure speed, accuracy and quality of performance, and some personality tests (Lindström, et al. 1976).

The results were compared with those of three different reference groups, one for the symptom questionnaire, one for nerve conduction velocities, and one for the psychological testing. All comparison groups were of a similar age and social class structure, and no referent had been exposed to neurotoxic substances. All those with a known history of head trauma, alcohol abuse, diabetes, epilepsy and other neurological diseases were excluded both from the exposed and the referent groups. The EEGs were not compared with any ad hoc control group, only with the laboratory's standard normal material.

Question 2

What do you think of the solution of not having one single reference group undergoing exactly the same examination? What do you think of the stepwise approach used for nerve conduction measurements?

Question 3

What is your opinion of not having any ad hoc reference group at all for the EEG examinations?

Question 4

Considering the level of knowledge in 1973, would you have added any further tests with the purpose of getting a more complete picture of neurotoxic effects? What tests would you employ today?

Based on the results from the first stage of the study, it was decided to use the urinary concentration of mandelic acid as the single exposure parameter. Urine was sampled at the end of the shift, once a week, at five consecutive weeks before the medical examination. The first week, sampling was made on Monday, the second on Tuesday, etc., and the mean value of the five measurements was used as the exposure parameter. The median of the individual means was 808 mg/l, and the range was 7-4715 mg/l. This median corresponds to a TWA of 33 ppm styrene in the air (see Fig. 8).

Question 5

What are the practical and medical aspects of using a biological parameter rather than an air sample as the exposure parameter?

The results of the medical examination showed significantly more symptoms among the exposed subjects, especially more fatigue, difficulties in concentration, and irritation of the mucous membranes. There was nothing remarkable in the physical examination. Slight differences were found in some psychological tests measuring visuomotor accuracy, psychomotor performance and lowered vigilance. In the neurophysiological examination the prevalence of abnormal EEGs was 24% which is clearly in excess of the 10% usually found in unselected normal materials. The criteria for abnormality were those used conventionally, and the EEGs were interpreted without knowledge of the exposure intensity and duration.

The pathology recorded was localized slow activity (14 cases), diffuse theta activity (8 cases) and bilateral spike and wave discharges (2 cases). The nerve conduction measurements did not reveal any slowing of conduction times. According to these results, the central nervous system (CNS) rather than the peripheral nervous system seemed to be the critical organ for styrene effects (as far as the nervous system is concerned) (Seppäläinen & Härkönen, 1976).

Question 6

What important bias is inherent in a study of this design? How does it affect (a) qualitative (b) quantitative interpretation?

PART 3

Quantitative aspects

In order to be able to study exposure-response relationships, the first decision to be made was what (a) exposure parameters and (b) what effect parameters should be used. It was already decided that the concentration of mandelic acid in the urine was the exposure parameter, so now the effect parameters remained to be selected.

Question 7

What principles would you apply for selecting effect parameters for quantitative purposes (i.e., exposure-response relationships)?

Application of the principles discussed in the answer to question 7 led to the selection of subjective symptoms, EEG findings and three psychological tests for scrutiny of exposure-response relationships. Of these, the frequency of subjective symptoms did not relate to the concentration of urinary mandelic acid, so this effect parameter was noninformative from a quantitative viewpoint.

Question 8

Why do you think no relation was found for subjective symptoms? Would you look at each symptom separately, or would you do something else?

The next issue was to decide in which way the exposure-response relationship should be explored for the promising-looking EEG findings and psychological tests. This involved two steps, i.e., (a) to find the most effective way of grouping the exposure parameter and (b) to classify the effect parameters.

Question 9

What different ways are there to do this? How would you proceed in finding the best categories of mandelic acid concentration?

Reduction of the data on the exposure response-relationship for abnormal EEG-findings, resulted in the subcategories of mean mandelic acid excretion shown in Table XLV and Fig. 9.

Table XLV. Distribution of subjects into categories according to their EEG findings and urinary mandelic acid concentrations. The statistical test results are derived from fourfold tables with cut-off points at the lower limit of the mandelic acid concentration category.

Mandelic acid concentration (mg/l)	Normal	EEG finding Abnormal	Total	% Abnormal	Chi^2	p
-- 699	34	4	38	11		
700-- 799	7	3	10	30	5.07	0.05
800-- 1199	10	7	17	41	3.66	(0.06)
1200-- 1599	8	3	11	27	0.30	NS
1600-- 1999	4	1	5	20	0.17	NS
2000-- 4779	10	5	15	33	0.36	NS
Total	73	23	96	24		

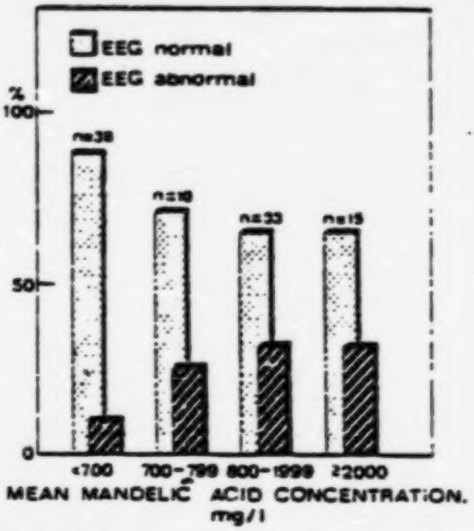

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Fig.9. Relative frequency of the normal and abnormal EEGs of the exposed subjects according to the urinary mandelic acid concentrations.

Question 10

What do you conclude from Table XLV and Fig.9?

In order to study the exposure-response relationship for psychological impairment those tests which showed the greatest between-group differences (not necessarily statistically significant) were selected. The tests were Symmetry Drawing, the Bourdon-Wiersma accuracy test (both describing visuomotor accuracy) and the Mira test (psychomotor performance).

Each test, as well as the mandelic acid concentration, was dichotomized. For Symmetry Drawing and the Mira test, the value equal to the mean + 1 standard deviation (SD) in the reference group was chosen as the cut-off point, because the number of persons with functions classified as poorer than the mean + 2 SD was too small. For the Bourdon-Wiersma test no data from the reference group were available; therefore the cut-off point was chosen from the exposed group itself in a similar manner. Calculations were then performed from fourfold contingency tables with cut-off points for mandelic acid concentrations of 800, 1200, 1600 and 2000 mg/l and Chi-square values were computed for every cut-off point. The cut-off points were derived in the same way as those for the EEG findings. Table XLVI shows the detailed data.

Table XLVI Distribution of subjects into categories according to their psychological test results and urinary mandelic acid concentrations. The statistical test results are derived from fourfold tables with cut-off points at the lower limit of the mandelic acid concentration category.

Mandelic acid concentration (mg/l)	Performance on psychological test				
	Better than or equal to cut-off value	Poorer than cut-off value	Total	Chi^2	p
Symmetry Drawing					
-- 399	20	2	22		
400-- 799	19	5	24	3.19	NS
800-- 1199	15	3	18	4.35	0.05
1200-- 1599	9	3	12	9.26	0.01
1600-- 1999	3	2	5	12.98	0.001
2000--	5	10	15	12.84	0.001
Total	71	25	96		
Bourdon-Wiersma Vigilance Test					
-- 1199	58	8	66		
1200-- 1599	10	2	12	1.76	NS
1600-- 1999	5	-	5	2.30	NS
2000--	9	6	15	5.36	0.05
Total	82	16	98		
Mira Test					
-- 1199	54	12	66		
1200-- 1599	9	3	12	4.59	0.05
1600-- 1999	3	2	5	6.39	0.05
2000--	7	8	15	5.59	0.05
Total	25	25	98		

For the Symmetry Drawing test a statistically significant difference was found when the mean mandelic acid concentration exceeded 800 mg/l (Chi^2 4.34, $p < 0.05$). The significance level of the Chi-square increased as the cut-off point for the exposure variable became higher. The Chi-square value reached its maximum at a cut-off point of 1600 mg/l (Table XLVI). The level of the Symmetry Drawing test results, at different levels of mean mandelic acid concentration, is shown in Fig. 10.

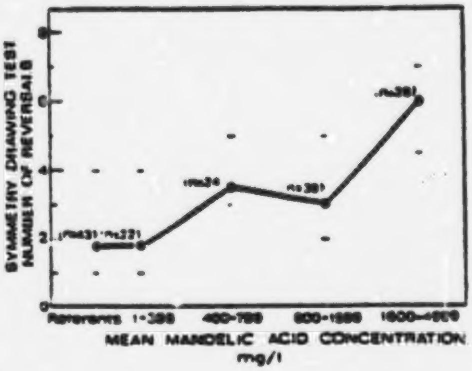

Fig.10.Median and interquartile range of reversals in the Symmetry Drawing test according to the urinary mandelic acid concentration.

As can be seen, there was a distinct increase in visuomotor disturbance as the mean mandelic acid concentration exceeded 1600 mg/l. The other variable of visuomotor accuracy, errors and omitted reactions in the Bourdon-Wiersma test, showed a reduced level only when the mean mandelic acid concentration was above 2000 mg/l (Chi^2 = 5.36, $p < 0.05$).

The results are shown in Fig. 11.

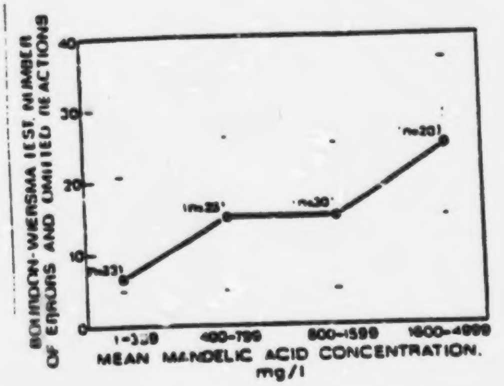

Fig. 11. Median and interquartile range of errors and omitted reactions in the Bourdon-Wiersma Vigilance Test according to the urinary mandelic acid concentration.

In psychomotor performance (Mira test) a statistically significant Chi^2 4.59, $p < 0.05$) decline occurred above the mean mandelic acid concentration of 1,200 mg/l (Table XLVI). Fig. 12 illustrates the relation between psychomotor performance and the exposure level.

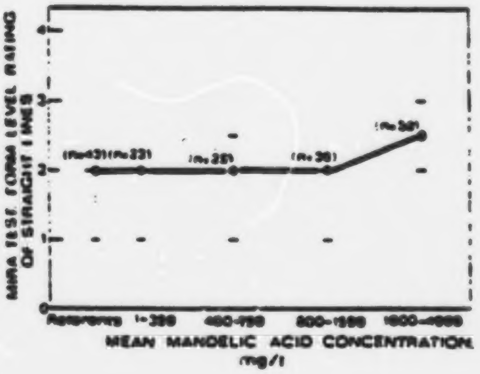

Fig. 12. Median and interquartile range of form level in the Mira test according to the urinary mandelic acid concentration.

Question 11

Would there have been alternative methods for showing an exposure-response relationship? If yes, why do you think the authors chose this method? Can you use psychological tests for within-groups comparisons, considering that age, primary level, education, etc., influence them?

Question 12

Considering that, out of a comprehensive test battery, these tests were the only ones showing impairment, what would you conclude about the severity of effects?

PART 4

Use of this study for standard setting

As already stated in the beginning, one of the main objectives of this study was to provide data which could be used for the setting of hygienic standards.

Question 13

Which was the lowest exposure level in terms of (a) urinary mandelic acid concentration (b) air concentration of styrene for which no effects at all could be shown?

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Question 14

Would you state that exposure below this level is safe?

Question 15

Provided you were able to define the noneffect level for all effects of styrene exposure, could that automatically be translated into a hygienic standard (eg, the TLV)?

INSTRUCTOR'S NOTES
STYRENE AND NEUROLOGICAL DYSFUNCTION

The first purpose of this exercise is to illustrate the thinking involved in research on exposure-response relationships, i.e., quantitative research. The second purpose is to give the students some ideas of the difficulties involved in standard setting. Next follows a short recapitulation of what sort of aspects should come up when the class attempts to answer these questions.

PART 1

Answer 1

At this stage the answer should address only why one should use the lower confidence interval for mandelic acid concentration (and the upper for styrene concentration in the air) and not the average when translating mandelic acid values into air concentrations of styrene, which are the only regulatory (or recommended in some countries) figures. Using the average mandelic acid concentration corresponding to the hygienic standard would mean that 50% of the workers would experience an exposure higher than the standard, be it the threshold limit value, maximal acceptable concentration, or some other standard. The lower confidence level means that 97.5% of the workers are exposed to less than the standard. The correct answer therefore is approximately 1000 mg/l of mandelic acid. Problems related to how to choose the variable, which best corresponds to average effects, are discussed under question 5, and the thinking involved in deriving a standard under questions 13, 14 and 15.

PART 2

Answer 2

Here one should discuss (1) the difference between a qualitative and a quantitative study, and (2) practical aspects (feasibility, economy).

While it is quite clear that one single, ad hoc reference group would be superior to any other solution in a qualitative study, a quantitative study actually compares different exposure categories within the exposed group, and for this exercise no reference group at all would be needed in a strict sense. However, normal data from some source are needed for dividing results into normal and abnormal. In the quantitative stage of this study reference values were used in this way.

As to practical aspects, it is hard to find unexposed groups willing to undergo a day-long examination, especially if psychological testing is involved, because this examination may be considered as interfering with personal integrity. It may be even harder to find employers who would allow the workers to be away from work one hundred or so days; hence one often has to compromise although validity inevitably suffers. Also, the reference group may increase the costs above the means of the investigator. So, one must consider thoroughly for what purpose the reference group, after all, is needed. What really is important in a quantitative study is to find a large enough exposed group and wide enough variations in exposure intensity and duration to permit enough subcategorizing.

The stepwise approach for nerve conduction measurements was far from ideal, because it rendered intragroup comparisons (e.g., combinations of "positive" symptoms) much more restricted. One would clearly prefer to have all the workers examined in the same way. Had there been "positive" findings for the nerve conduction velocities, their interpretation had been very difficult with this approach, and no useful exposure-response data would have emerged.

Answer 3

Much has already been said about this in the answer to question 2. Here it would suffice to stress the importance of not using laboratory reference values as the only basis for comparison. In a qualitative study one should never accept X% "pathological" values as proof of effect, without any comparison with a reference group. On the other hand, laboratory reference values may provide some sort of standard for dichotomizing within the exposed group. Then the intention is not to show qualitative effects, but to provide contrasts.

Answer 4

This is a trap. Most physicians would be eager to add an almost infinite number of (unnecessary) examinations. A thorough discussion of the advantages and disadvantages of loading the study with a great number of medical examinations is warranted. In 1973, styrene toxicity was not well known in the occupational setting, and this could have tempted the inclusion of more examinations for the purpose of having a fruitful "fishing expedition". However, this would have increased costs, endangered cooperation, and made the problem of finding reference groups even more difficult. Here one should also discuss the pro's and con's of restricting the study to the nervous system (pro's: study easier to handle, advance hypothesis existing, con's: possibility to overlook something important, possibility that some other effect would have been even more sensitive). One cannot solve all the problems in occupational medicine by one single study.

Nowadays, one could be tempted to use a computerized transaxial tomographic (CAT)-scan and other sophisticated modern methods for studying the CNS. If so, because of the costs involved it would be prudent to select only the most exposed ones, or only those with other effects present, at the first stage, which then would be qualitative. This would need a reference group. Whether or not a quantitative study should meaningfully employ a CAT-scan would then depend on the findings of the qualitative study (note here both the danger of circular reasoning and negative bias due to selection). A stepwise advance would involve asking some subjects to attend examinations twice.

Perhaps the most important point to stress is that the exposure side is at least equally important as the effect side in a quantitative study. Rather than overloading such a study with sophisticated clinical examinations one should put the greatest effort into securing valid and representative exposure data, and any possible extra funds should therefore be used for this purpose.

Answer 5

There is a strange persisting habit of relating the results of biological exposure tests first to air concentrations, then the air concentrations to effects, and finally, via this byway, biological tests to effects. This sort of nonsense probably has its roots in TLV-philosophy, i.e., biological tests are useful only if they correlate with air concentrations, because then and only then "protection" can be ensured. Nothing could be more erroneous. The only logical method would be to correlate biological tests directly with the effects, because the biological tests reflect the absorbed dose better than any air samples. In addition they are more practical to utilize than air measurements for this purpose.

In this example only the average concentration of mandelic acid in urine during a five-week period was used as the exposure parameter. Why was not the exposure time considered? In fact, the authors tried to incorporate this variable into an exposure index (mandelic acid concentration times months of exposure), but this did not work. There are several reasons for this. One is selective drop out, as discussed elsewhere (e.g., in question 6). Another is that there are no reasons to assume that the five week period studied is representative of exposure levels and working situations several years ago. Still another is that some of the effects indeed may be subacute and therefore current exposure may explain them better than cumulative exposure.

Answer 6

The most severe bias is selection out from exposure, which results in dilution of the effects. Styrene exposure causes both narcotic symptoms and irritation of the mucous membranes. Workers who cannot stand these symptoms are prone to seek other types of work. A Finnish study on car painters has shown that about 30% of those who had left the occupation reported health effects as the most important reason for quitting (Husman, 1980). However, it is not known to what extent subjective symptoms are predictive of EEG changes and psychological impairment, so the real effects of the health-based selection upon these parameters is impossible to tell.

The same selection bias also decreases the correlation between exposure and effects, because those most affected may drop out especially at higher exposure levels.

PART 3

Answer 7

Here one should address principles only. Procedural matters are addressed in question 9. In the first stage one would always prefer those examinations which showed qualitative differences. However, it may well be that the threshold for some effects is so high that only the most exposed subjects show abnormal values. Then nothing may be revealed when the whole groups are being compared. Therefore all tests used should be looked at by exposure categories (say, three or four equally-sized groups), with special attention given to the highest one.

If differences exist, either between the entire groups or when comparing the highest category with the referent group or with lower categories, the next step would be to construct proper exposure-effect or exposure-response curves.

In this context someone may ask what the difference is between an exposure-effect and an exposure-response curve. The Task Group of Metal Toxicity (1974) has defined "effect" as a "biological change caused by an exposure" (Nordberg, 1976). When data are available for both exposure and effect on a graded scale, an exposure-effect relationship can be established. The term "response" was defined as the proportion of a population that demonstrates a specific effect (in this case, e.g., abnormal EEGs). A short discussion on the difference between an exposure-effect versus an exposure-response relationship may be warranted here. The exposure-effect relationship exhibits an average effect in all individuals, provoking the false impression that the population is homogeneous. By contrast, an exposure-response relationship takes into account the variation in susceptibility within groups of individuals since it indicates the proportion of persons showing abnormal values. For preventive purposes it is extremely important to be able to define the most sensitive individuals in a population.

In this example only responses are dealt with. Had nerve conduction velocities been of quantitative interest both effects (mean values) and responses (proportions with abnormal values) could have been scrutinized.

Answer 8

Subjective symptoms are nonspecific and vague. However, according to cumulative evidence, not available in the mid 1970s, some questions (sleepiness, concentration difficulties, forgetfulness) tend to be more typical of solvent effects than others. Because of the nonspecificity of the subjective symptoms, there is much "background noise", and therefore this material probably is too small for revealing any exposure-response pattern, if such a pattern indeed exists.

Another explanation could be that subjective symptoms lead to selective drop-out, especially from the higher exposure categories. The most resistant individuals would be those most likely to remain exposed, and they would not complain of many symptoms. Furthermore, those used to work at regularly high exposure levels tend to regard many symptoms as normal, while those occasionally exposed to peaks would react in a stronger way. The former group would have high mandelic acid concentration, the latter relatively low.

Alternatives to using single symptoms would be to group similar types of questions, or scoring the answers (e.g. one score per positive answer), but both these methods have shortcomings. It is not unequivocal to group questions, and when scoring, should the same weight be given all questions? What about questions from other areas than CNS functions? Scoring would also emphasize those who tend to answer "yes" to almost everything.

Answer 9

One could group the workers according to categories of mandelic acid concentrations. Two or more groups could be tried. One way would be a subdivision from the median value, yielding two equally sized group, or forming three or more groups according to the same principle. A more efficient way would be to search for the cut off points yielding the best statistical power (this is further considered in subsequent answers). Another approach would be to construct a correlation diagram from numerical values. This would require numerical values or at least several classes for the effect parameter also. However, the parameters used in this study were dichotomized, and therefore correlation analysis could not be applied.

The decision of how to dichotomize the effect variables into "normal" and "abnormal" is an arbitrary one. Often the mean value plus or minus two standard deviations (SD), derived from a reference population, is used. There is nothing saying that this is the only correct solution. In this study, for example, plus 1 SD was used for two tests because plus 2 SD would have resulted in so few abnormal subjects that calculations would not have been possible. For the third test no reference group was available; therefore the cut-off point had to be chosen from the exposed group in a similar way. This approach may be criticized; however, the point was not to diagnose abnormalities, but to create contrasts for internal comparisons. Quite another approach was used for the EEGs: here conventional clinical criteria were used (no mean values are possible for EEG findings). It can be added that applying the same criteria yields about 10% "abnormal" results in an unselected general population (Härkönen, 1977).

Table XLV is a condensed result of looking for the most efficient way of forming subcategories. This was done in the following way (it may be useful to prepare a transparency in advance):

Search for a concentration level above which abnormal EEGs begin to occur
(four-fold tables with different mandelic acid categories)

STEP 1.

EEG abnormalities	Mandelic acid conc., mg/l < 100	> 100	Total	
no	7	66	73	
yes	-	23	23	Chi^2= 1.17
	7	89	96	p=NS

STEP 2

	< 200	> 200		
no	11	62	73	
yes	1	22	23	Chi^2=0.99
	12	84	96	p=NS

STEP 3

	< 300	> 300		
no	15	58	73	
yes	2	21	23	Chi^2=0.97
	17	79	96	p=NS

STEP 4

	< 400	> 400		
no	21	52	73	
yes	2	21	23	Chi^2=2.84
	23	73	96	p=NS

STEP 5

	< 500	> 500		
no	25	48	73	
yes	4	19	23	Chi^2=1.62
	29	67	96	p=NS

STEP 6

	< 600	> 600		
no	29	44	73	
yes	4	19	23	Chi^2=2.91
	33	63	96	p=NS

STEP 7

	< 700	> 700		
no	34	39	73	Chi^2=5.07
yes	4	19	23	$p < 0.05$
	38	58	96	

STEP 8

	< 800	> 800		
no	41	32	73	
yes	7	16	23	Chi^2=3.66
	48	48	96	p=NS

(p<0.06)

STEP 9

	< 900	> 900		
no	44	29	73	
yes	10	13	23	$Chi^2=1.38$
	54	42	96	NS

	< 1000	> 1000		
no	46	27	73	
yes	12	11	23	$Chi^2=0.47$
	58	38	96	p=NS

According to this, it seems that 700 mg/l is a level, under which the proportion of EEG abnormalities remains low, and above which the prevalences stay on a rather stable level of about 30%.

In Table XLV the categories of 0-399 and 400-799 were split differently to show the cut-off point. This table could also be constructed in the following way without loosing much information:

Mandelic acid mg/l	N	EEG abnormalities n	EEG abnormalities %	Chi^2
0 - 699	38	4	11	5.07
700 -	58	19	33	$p<0.05$
Total	96	23	24	

or perhaps:

	N	EEG abnormalities n	EEG abnormalities %
0 - 699	38	4	11
700 - 1399	34	12	35
1400 -	24	7	29
	96	23	24

but the latter design would not, after all, add much information. It is evident from Table XLV that there is no trend, only a threshold. Therefore it is not meaningful to use a test for a trend. Regression analysis cannot be applied to this material, either, because the dependent variable is dichotomous.

Answer 10

The subcategory with a mean mandelic acid excretion of less than 700 mg/l has a rather normal frequency (about 10%) of pathological EEG findings, while all other groups have 20-40%. The same pattern is shown in Fig. 9, which also shows a leveling off after the initial rise. Hence one can say that 700 mg/l is the point estimate for the threshold, and that no further increase in pathology occurred after this threshold, in other words, there was no trend. This is not a typical exposure response curve, but one must consider that exposure was measured during five weeks only.

An index, based on intensity times duration was tried, but it did not change the results. Indeed, there is little justification for the assumption that present exposure levels would describe past levels satisfactorily. Hence, in spite of figures, the exposure was actually not very well described. This is a good example of a serious drawback in almost all hitherto published quantitative studies in occupational medicine. Improving the documentation of exposure would therefore be much more important than further sophistication of medical examinations in future studies.

Answer 11

For the psychological tests, yes, there would have been alternative methods. These results were actually first analysed by means of a multiple regression analysis (Lindström, et al. 1976) which gave virtually the same results. However, the results are more comprehensible if shown in a simpler way. There is no rationale for expressing results in a complicated way, if the same message can be conveyed in a simpler way. Comprehensibility is especially important in studies like this one, whose results hopefully will be used by administrators for standard setting.

However, a multiple regression analysis is not the only alternative. One could also use a test for trend in proportions. With hindsight, it was a mistake not to show this statistic, which actually was done. All the three psychological tests concerned showed a statistically significant trend (Symmetry)drawing: $Z= 4.09$, $p< 0.001$, Mira: $Z= 2.89$, $p < 0.01$, Bourdon-Wiersma: $Z=3.24$, $p< 0.01$).

As to whether or not an examination which is vulnerable to potential confounding, can be used for within-group comparisons, the answer is that one must first rule out confounding. This was done in the present example. Age did not correlate with the exposure level in this material, so it was no confounder (stress the conditions for confounding; i.e., association with both exposure and effect), and the primary intelligence level of many of the subjects had been checked, while they did their military service at the age of 19 years. There was no correlation between primary level and exposure intensity. The educational level was rather homogeneous within the group.

Answer 12

Although this was the first epidemiological study showing that styrene exposure indeed can cause CNS-effects, it must be underlined that the findings were mild and restricted to a few psychological functions only (Härkönen, et al. 1978). On the other hand, one must realize that this was a cross-sectional study. Such studies are always hampered by selective turnover,which serves to mask existing effects. In spite of this, several different indications of CNS function impairment occurred in the same group of workers. Moreover, the exposure-response relationships found strengthen the probability of that the association found between exposure and effects really was causal.

PART 4

Answer 13

The earliest changes (increased EEG pathology) occurred when the mandelic acid concentration rose above 700 mg/l, and the first psychological impairments were seen at 800 mg/l. These values correspond on an average to 30 ppm of styrene in the air (Fig. 8), but if one takes the lower confidence limit, the corresponding value is about 12 ppm. Here it would be worthwhile to discuss different approaches and their implications in extrapolating to air concentrations (maximal safety versus best guess). Maximal safety would imply using the lower confidence level, which would result in health-based recommendation for an air standard of about 10 ppm. If EEG effects are considered serious, some safety margin would even be warranted. On the other hand, one single study cannot be relied on too strongly, because of all the uncertainties involved in epidemiological research (e.g., inexact exposure assessment, bias, nonspecific measures of effect, etc.), so one would be a little reluctant to press hard on dramatic changes in prevailing standards merely on the basis of these results. The "best guess" of 30 ppm could therefore also be defended as a health-based recommendation. Irrespectively of whichever approach one uses, the American Conference of Governmental Industrial Hygienists' (ACGIH) documentation (1976) on TLV of 100 ppm, recommended in the 1970s, is far to high to prevent CNS symptoms. It has now been lowered to 50 ppm, which still seems to be rather high.

Answer 14

Two groups of arguments should be discussed here. The first group consists of weaknesses in this specific study, such as hazy exposure data (especially regarding past exposure), effect of selection, nonspecificity of responses, etc. Also difficulties in extrapolating from biological to air levels should be discussed. The conclusion, of course, is that several uncertainties prevent any firm statements even with regard to the very effects this study was designed to investigate.

As to complete safety, one must regard all types of effects. Since the mid-1970s there has accumulated suggestive evidence on the genotoxicity of styrene. If styrene indeed is carcinogenic, then studies on CNS effects are of very limited value for standard setting.

Answer 15

This question is included to illustrate the two-step procedure in standard setting. First, the health based noneffect level should be established in a scientific way. Unfortunately this exercise is often hampered by lack of sufficient data, especially exposure data. But in any case this is the first step only in standard setting. Scientists should never, on the basis of their own, single study, try to tell the world what the TLV should be. This recommendation can only be given after the second step, where administrative, technological, economical and policy questions should be considered by the communities decision-makers (labor unions, employers, government representatives, technological and scientific experts together).The administrative standard is the combined result of all these considerations. Hence the administrative standard is usually not a sharp border between total safety and the start of occurrence of effects. Often the administrative standard accepts some degree of effects, but sometimes there is even a margin of safety. It is often a compromise between health demands and technological and economical feasibility. American classes may ponder on to what extent the documentation (1976) on TLV prepared by the ACGIH complies with this two-step procedure, and all classes could finally try to list those substances for which there exists sufficient scientific knowledge for health-based recommendations. That list would be extremely short.

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308

OCCUPATIONAL ASTHMA DUE TO PLATINUM SALTS*

PART 1

In January 1981, the National Institute for Occupational Safety and Health (NIOSH) received a request from the United Steel Workers of America, Local 7836, a trade union, to evaluate the respiratory effects of exposure to platinum salts. Workers represented by the union are employed in a secondary refinery of precious metals. The 12-year old facility reclaims platinum and other precious metals from scrap metal and expended catalyst used in the electrical and chemical industries. The scrap is burned, milled, and then dissolved in aqua regia (a mixture of hydrochloric and nitric acids). The precious metals are separated and concentrated through sequential solubilization and precipitation to yield ammonium hexachloroplatinate or "yellow salt." The salt is then heated to result in metallic platinum. Workers exposed to platinum salts during this process reportedly develop sneezing, watery eyes, cough and asthmatic wheezing. The union noted that a large number of workers had been medically terminated from employment after developing symptoms of allergy.

After receiving this request, the investigators reviewed the medical literature on platinum toxicity. In summary, Karasek and Karasek in 1911 first reported the development of allergic rhinitis, dermatitis, and bronchial irritation among workers exposed to platinum salts. Studies by Hunter and coworkers (1945) and by Hughes (1980) have confirmed the potential of platinum salts to induce allergic reactions. Up to 60% of workers exposed to levels of 2 to 200 ug Pt/m^3 become sensitized with a latency of three months to several years after first exposure (Proctor & Hughes, 1978). Laboratory studies have found that sensitization develops to the halogenated salts of platinum (e.g., ammonium hexachloroplatinate) and not to the metal itself (Cleare, et al. 1976; Cromwell, et al. 1980). Bronchial challenge tests with the platinum salts can produce immediate, late, or dual responses in sensitized individuals (Pepys & Hutchcroft, 1975). Tests using laboratory animals suggest that the allergic reaction is mediated primarily by IgE (Pepys, et al. 1980). Complete recovery is believed to occur after removal from exposure (Hughes, 1980). While some studies of platinum allergy have been completed in Europe, the problem has received virtually no attention in the United States of America.

Question 1

Discuss the clinical patterns and mechanisms of occupational asthma as they relate to the design of an epidemiological study of the problem.

Question 2

List other agents known to cause occupational asthma.

Question 3

How would you proceed initially to define the nature and magnitude of the health problems at the facility?

a) What would be the key factors you would assess?
b) What sources of information you would use?

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* By Dean Baker, 1985; revised December 1985.

PART 2

After an initial meeting with union and management and tour of the facility, the investigators arranged to review all records pertaining to the number of workers at the facility, potential exposures, medical testing procedures, and documented the health problems. The facility currently had 122 employees, one-third of whom worked in offices with no apparent exposure to platinum salts. The investigators abstracted personnel records of all employees who had been terminated due to medical reasons. The number of medical terminations by work area at time of termination is shown for 1974 to 1979 in Table XLVII.

Table XLVII Terminations due to bronchitis and dermatitis
(number of employees terminated by year)

AREA	1974	1975	1976	1977	1978	1979
Refinery	2	4	5	4	2	3
Recovery	1	3	3	1	0	0
Maintenance/ warehouse	1	1	2	0	0	1
Chemical products/ salts	1	3	1	0	4	0
Laboratories	0	0	0	0	0	1
Other	0	2	2	0	0	0
Total	5	13	13	5	6	5
Total employees on site	125	130	150	175	147	140
Total employees in operating areas	66	65	93	96	80	108
Proportion terminated in operating areas	___	___	___	___	___	___

Question 4

Calculate the proportion of workers in the operating areas per year who were medically terminated due to bronchitis and dermatitis.

a) Do these results suggest that there is a medical problem?

b) Why might one use the number of employees in the operating areas (rather than total employees) as the denominator of the proportion?

c) The proportion of workers being medically terminated per year tends to decrease over time. What could be explanations for this trend?

d) How useful is the information on the number of terminations by last work area? What additional information would you want to determine?

Little data on exposures to platinum salts within the facility were available. The company could provide environmental monitoring data for various areas of the facility for the years 1977 to 1979. Some examples of the monitoring data are shown below in Table XLVIII.

Table XLVIII Examples of industrial hygiene sampling results for platinum salts

Date	Location	Air concentration (per m^3)	Sampling time(h)
28 Jun 1977	Warehouse	11.5 ug	0.85
		2.3 ug	1.57
		3.5 ug	1.83
4 Aug 1977	Recovery, 3rd & 4th floors	5.0 ug	0.92
		25.0 ug	1.63
		120.0 ug	1.00
11 Oct 1977	Refinery, cascade	34.0 ug	4.65
13 Sep 1979	Refinery, muffle room	1.6 ug	1.58
		0.8 ug	4.00

The results of environmental sampling usually are expressed as a time-weighted average (TWA) of the air concentrations for an entire work day. The formula for a time-weighted average is as follows:

$$\text{TWA Concentration} = \frac{\sum_{i=1}^{N} (\text{Concentration Sample } i) \times (\text{Time Sample } i)}{\sum_{i=1}^{N} (\text{Time Sample } i)}$$

where N = number of samples taken in area over the workshift.

Question 5

Calculate the TWA air concentrations of platinum salts for the four days of sampling listed in Table XLVIII.

a) What are the assumptions implicit in the use of the TWA formula?

b) Given that the examples in Table XLVIII are typical of the other sampling results, do you believe a potential environmental hazard exists at the facility? What other information is necessary to assess the actual level of exposure to the employees?

Finally, the investigators reviewed the medical services for the facility, including pre-employment and periodic medical screening procedures. Prior to 1979, pre-employment screening consisted of a general medical history and physical examination. Since April 1979, potential employees also have been evaluated for general histories of allergies and specific platinum salt sensitization. Persons with positive allergy tests were not hired. Periodic screening consists of a interim medical history and physical examination. Since 1977, chest radiographs have been obtained every two years and pulmonary function tests every year. Skin prick testing for platinum salts sensitization is not routinely done. Workers who complain of symptoms to the company nurse are referred to local physicians for a medical evaluation, including pulmonary function tests and skin testing with platinum salts; those with positive skin tests are medically terminated.

Question 6

Discuss the adequacy of the medical screening procedures. How might these procedures result in a biased documentation of allergic disease among the exposed workers?

After reviewing existing personnel and medical records, environmental sampling results, and medical testing procedures, the investigators decided to conduct a cross-sectional medical evaluation of workers potentially exposed to platinum salts.

Question 7

Who would you ask to participate in the study?

Question 8

What specific tests would you include in a field medical evaluation of allergic occupational asthma?

PART 3

The investigators decided to conduct a cross-sectional medical evaluation of all current employees and any ex-employees who were medically terminated due to asthma, bronchitis, or dermatitis. Each subject would be be given a questionnaire on present health symptoms, past medical history, family history of allergy, and work exposure history; a physical examination of the heart, lungs, and skin; spirometry (lung function tests) before and after a work shift (current employees only); pulmonary cold-air challenge test; skin prick testing to platinum salts and three common aeroallergens (ragweed, timothy, and dust); and blood drawing to measure serum concentration of total IgE and of IgE specific for common allergens using a radioallergosorbent test (RAST). The pulmonary cold-air challenge tests consists of spirometry before and after the subject vigorously breathes air cooled to -40°C; it is designed to elicit nonspecific hyperreactivity of the bronchial airways - a condition indicative of bronchial asthma.

Question 9

How would you trace and contact the medically terminated workers?

Question 10

Since the evaluation includes breathing tests and the collection of a blood sample, it is possible that workers may be reluctant to participate. What steps would you take to maximize voluntary participation?

Question 11

The investigators felt that there were insufficient resources to allow them to duplicate the study on unexposed workers at another facility as a comparison (referent) population. How would you establish a referent population in this situation?

PART 4

During the Summer of 1981, NIOSH investigators arranged for researchers from the University of Cincinnati to provide expertise in conducting the cold-air challenge tests and skin prick and blood tests for allergy. Arrangements were made for NIOSH trailers to be parked at the facility so that the employees could be tested on-site. Based on a review of the medical records, the investigators decided that 49 workers had been terminated possibly due to platinum salts allergy; they used telephone books, motor vehicle license records, and interviews with current workers to trace the terminated workers. Thirty-six terminated workers were located; 29 agreed to participate in the study.

In September 1981, the investigators from NIOSH and the University of Cincinnati conducted the medical evaluation of the terminated workers and 107 (87%) of 123 available current employees. Nine employees were not available due to vacations or illnesses.

Question 12

What potential biases may arise from studying only 29 of 49 medically terminated workers? How could you evaluate the potential bias?

Question 13

Nine current workers were unavailable at the time of the study and 16 elected not to participate in the evaluation. How might these non-participants affect the results of the study. How would you evaluate the potential impact of the non-participation?

Fifteen (14%) of 107 current employees and eight (28%) of 29 terminated workers had positive platinum salts skin tests. This study was the first to find persistent positive skin tests among medically terminated workers.

Question 14

As noted above, the literature states that sensitivity to platinum salts resolves once exposure has ceased. How do you explain the discrepancy between the literature and the results of this study?

PART 5

Initial analyses of the data focussed on the relationships between the skin prick test for platinum salts; symptoms of asthma, rhinitis, and contact dermatitis; positive cold-air challenge test; elevated total IgE; atopic tendency as indicated by positive skin test to the aeroallergens; and smoking status. The variable definitions are as follows:

Rhinitis symptoms - Itchy, watery eyes or itchy, runny nose while at work.

Asthma symptoms - Wheeze plus two-thirds of whom have a cough, shortness of breath or chest tightness.

Reported dermatitis - Itching or burning skin while at work.

Positive cold air test - Decrease in the forced expiratory volume in one second $\geq$ 9% after cold-air challenge.

Elevated IgE - Total IgE > 500 ng/ml.

Atopic status - Positive skin test to $\geq$1 of ragweed, timothy, or dust.

Initial results are presented in Table XLIX. Each outcome except smoking has been dichotomized (i.e., positive or negative) for ease of presentation. The test results are presented separately for current workers who were platinum salts skin test negative; current workers who were platinum salts positive; and all terminated workers.

Table XLIX Test results by status and platinum skin test

Reported symptom or test result	Current workers Pt. skin test Number	%	Current workers Pt. skin test + Number	%	Terminated workers Number	%
Rhinitis symptoms	28/92	30	13/15	87	10/29	34
Asthma symptoms	29/92	32	9/15	60	11/29	38
Reported dermatitis	7/92	8	4/15	27	6/29	21
Positive cold-air test	6/85	7	5/15	33	8/27	30
Elevated IgE	7/87	8	4/15	27	9/29	31
Positive atopic test	29/92	32	6/15	40	8/29	28
Smoking - current	31/91	34	12/15	80	20/29	69
- quit	24/91	26	2/15	13	8/29	27
- never	36/91	40	1/15	7	1/29	3

The relative risk of an adverse health outcome due to platinum salts allergy was estimated by calculating the odds (cross-product) ratio for each outcome among the platinum salts skin test positive versus negative current employees.

Question 15

In cross-sectional prevalence studies, when is the prevalence odds ratio (cross-product ratio) the appropriate measure of effect and when is the prevalence ratio the appropriate measure of effect? Why was the prevalence odds ratio used in this study?

Question 16

Calculate the prevalence odds ratios for each health outcome among platinum salts skin test positive versus negative current employees. Is platinum salts sensitivity an apparent risk factor for these adverse health outcomes?

Question 17

Interpret the results of the atopic test and smoking status as they relate to platinum salt allergy.

a) Is smoking habit an apparent risk factor for platinum salts allergy?

b) Is atopic tendency an apparent risk factor for platinum salts allergy?

c) How do these findings influence your analysis and interpretation of the effect of platinum salts allergy on the health outcome variables?

Question 18

You know (from the literature review) that the skin prick test is a highly specific, but not highly sensitive test for platinum salts allergy. How would the lack of sensitivity of the skin prick test influence the apparent relationship between platinum salt allergy and the results of the other tests mentioned above?

Question 19

The questionnaire also asked about the time of onset of symptoms; thus, it is possible to separate the workers with symptoms into those with onset before or after beginning work at the facility. As an example, this division for asthma symptoms among current workers is shown below:

	Positive asthma symptoms		No symptoms
	Onset before hire	Onset after hire	
Pt. skin test +	1	8	6
Pt. skin test -	17	12	63

a) How does a consideration of the time of onset of the asthma symptoms influence the apparent association between the symptom and the platinum salts skin test results?

b) In analysing the data, how should you treat the 18 persons who reported having asthma symptoms prior to hire at the facility?

Question 20

A criticism of cross-sectional epidemiological studies is that usually the study population is a "survivor population." How does the inclusion of the medically terminated workers in this study affect your ability to interpret these data? Use data in Table XLIX to substantiate your argument.

INSTRUCTOR'S NOTES
OCCUPATIONAL ASTHMA DUE TO PLATINUM SALTS

Summary

This cross-sectional medical evaluation attempted to overcome the limitation of studying only a "survivor" population by including workers who had been medically terminated from the facility in prior years. The mechanisms for tracing and the value of including these ex-workers are presented. The emphasis of the exercise is on the interpretation of data and the recognition of potential biases arising in cross-sectional epidemiological studies. Major didactic points include:

A. The causes of occupational asthma.
B. Calculation and interpretation of time-weighted averages.
C. Field (on-site of facility) methods for evaluating occupational asthma.
D. Methods to trace ex-employees for participation in a medical evaluation.
E. Interpretation of study results and recognition of potential biases, including reporting errors, loss to follow-up, non-participation, and misclassification.
F. Appropriate measures of effect in cross-sectional morbidity studies.

PART 1

Answer 1

The discussion of mechanism should be adjusted to the clinical training level of the participants. The discussion should emphasize the clinical features and mechanisms that are relevant to the design and interpretation of an epidemiological evaluation - i.e., clinical patterns by symptoms and timing, latency after exposure, predisposing factors, and pathophysiological mechanisms as they influence the medical testing procedures.

Definition. "Asthma is a disorder of function characterized by widespread partial obstruction of the airways which varies in severity, is reversible either spontaneously or as a result of treatment, and is not due to cardiovascular disease." (Ciba Guest Symposium Report, 1959). It has been estimated that about 2 % of all cases of asthma are due to occupational exposures. The investigator must take care to differentiate between occupational and nonoccupational asthma.

Clinical patterns. The major patterns of asthma include "immediate" (develops within minutes after exposure with recovery usually within minutes to a few hours); late or "nonimmediate" (usually starts several hours after exposure and is maximal for four to eight hours); or dual (occurrence of both immediate and late types together). Questionnaires must attempt to elicit the time pattern of symptoms. If any medical testing is planned, it must be appropriate to the pattern of the asthma (e.g., reaction during the workshift or, perhaps, at home after the work shift).

Latency. Allergic asthma does not occur on first exposure. The latent interval after first exposure varies from a few weeks to many years. Several studies report sensitization in workers after episodes of very high exposure. Nonallergic asthma reactions may develop at any time with sufficient exposure. Questionnaires should assess the timing of onset relative to first exposure to potential agents and should evaluate whether symptoms developed after a particularly high exposure. The investigator should keep in mind that average exposure may not be the most relevant index of exposure.

Predisposing factors. Atopic individuals (those with a tendency to produce IgE antibodies readily on contact with common environmental allergens) are at increased risk of sensitization due to some agents (e.g., grain dust, biological detergents), but not to others. Likewise, smoking may predispose individuals to the development of asthma after occupational exposures. Questionnaires should evaluated these factors.

Mechanism. Most instances of occupational asthma are due to Type I or immediate hypersensitivity reactions mediated by IgE, or in some instances by short-term sensitizing IgG antibody (S-TS IgG). Contact with the allergen causes release of histamine from mast cells, which in turn stimulates smooth muscle contraction in the airways. Both IgE and IgG antibodies can be measured using existing immunological techniques, such as the skin prick test. In some cases bronchoconstriction may be caused by complement activation, irritation, or nonimmunological release of histamine. These mechanisms are not mediated by antibodies and can not be evaluated using standard skin tests.

Treatment and prevention. Treatment of occupational asthma is not satisfactory in the presence of continuing exposure. Generally sensitized workers must be removed from exposure. Prevention usually involves a combination of the following strategies - substitution, environmental controls, use of personal protective equipment, identification of susceptible workers (when relevant for the particular exposure), and periodic medical examinations.

Answer 2

Many agents have been identified as causing occupational asthma. Some examples are listed below, with the occupations generally affected.

a)	Grains, flours, plant and gum	
	Grain, flour, hops, castor beans, gum acacia, wool	Bakers, millers, farmers, grain elevator operators, printers
b)	Insects, etc.	
	Beetles, locusts, cockroaches, grain weevil, grain storage mites, moths and silkworms	Laboratory workers, entomologists, farm workers, mill workers, anglers
c)	Laboratory and other animals	
	Rats, mice, guinea pigs, rabbits, avian proteins, feathers, prawns	Laboratory workers, bird fancers, prawn processing, oyster shuckers

d)	Fungi Spores of various fungi	Bakers, farm workers, domestics
e)	Woods Western red cedar, South African boxwood, oak, mahogany, redwood	Wood workers, carpentors, pattern makers, wood finishers
f)	Metals Boranes, chromic acid, platinum salts, potassium dichromate, nickel, vanadium, cobalt	Chrome plater, cement workers, platinum refiners, chemists, welders, grinders
g)	Chemicals Fluorine, tannic acid, various amines, formalin, trimellitic anhydride, colophony	Chemical workers, nurses, paint sprayers, laboratory workers, solderers, meat wrappers
h)	Drugs and enzymes Psyllium, methyl dopa, penicillins, tetracycline, trypsin,pancreatic extract, *Bacillus subtilis*	Drug manufacturer employees, chemists, pharmacists, detergent manufacturer workers
i)	Isocyanates Toluene diiocyanate	Workers on toluene diiocyanate manufacturer, plastics factory, foam manufacture, toy makers.

Answer 3

The investigators should attempt to verify the diagnoses of identified cases and to define the magnitude of the problem through the construction of prevalence or incidence rates. The investigators should talk with all concerned parties and review existing records to assess the potential exposures, population at risk (denominator of rate), and health events of interest (numerator of rate).

a) Potential exposures - production process; substances present in the facility (raw materials, intermediate and final products); past exposure monitoring (and results); ventilation and engineering controls; work practices; use of personal protective equipment; hygiene practices, such as where workers eat and smoke; etc. Much of this information is best interpreted by an industrial hygienist, who should work together with the epidemiologist.

Population at risk - number of employees over time by work areas and possibly by job titles; turnover rates (total, voluntary, and involuntary for medical or other reasons).

Health events - symptoms and known medical conditions among workers; absenteeism rates; use of medications; number and causes of medical terminations.

b) Sources of information include the following:
Potential exposures - facility environmental monitoring procedures and results; facility procedures for work practices, ventilation system maintenance, use of personal protective equipment, etc.; results of previous investigations by other agencies (e.g., OSHA or NIOSH); company production records, sales records, raw material purchase records, and brochures; and detailed discussions with workers, management, and safety officers on potential exposure sources.

Population at risk - primary source of information is the personnel records of the facility (group records from payroll for denominators of rates and individual records for job titles, work areas, and length of employment); other sources include union dues check off and direct verification through counting or listing of employees (practical, only if a relatively small facility)

Health events - legally required records (e.g. OSHA 200 forms), facility medical records (may have to go to local physician's office to review); nurses station log; workers' compensation and medical insurance, if plan exists; and focussed group discussions with management, medical service providers, local medical practitioners, nurse, and workers on their views of the health problems.

PART 2

Answer 4

The proportion of workers in the operating areas per year who were medically terminated due to bronchitis or dermatitis is shown below:

1974	1975	1976	1977	1978	1979
5/66	13/65	13/93	5/96	6/80	5/108
0.076	0.200	0.140	0.052	0.075	0.046

a) The results clearly suggest that there is a medical problem; 0.098 or nearly 10% of the workers in the operating areas per year were terminated after developing bronchitis and/or dermatitis.

b) The employees in the nonoperating areas generally are not exposed to the platinum salts and, thus, effectively are not at risk of developing allergy. By including them in the denominator of the calculation, one would underestimate the true risk of being medically terminated due to platinum salts exposure.

At this stage of the evaluation (descriptive epidemiology), the strategy is to continually refine the numerator and denominator of the prevalence or incidence rates to improve the estimate of risk. Numerators are made more precise through case verification and refinement of the case definition. Denominators are refined by attempting to identify the actual population at risk. In this case, the investigator used the employees in the operating areas as the best initial estimate of the population at risk.

c) Interpretation of preliminary data is problematic; however, the investigator should consider the following possibilities: 1) there is an artifact; 2) the data are spurious due to reporting bias; and 3) the data reflect true biological events. The students should be encouraged to identify as many possibilities as they can. The instructor should emphasize the need to critically interpret data. Possibilities for the observed trend include:

Artifact. Perhaps there is no true downward trend: a) the numbers used to calculate the proportions are relatively small and, thus, unstable. If only a few of the 13 persons terminated in 1975 had been terminated a few months earlier in 1974, the proportions would have evened out, eliminating the peak proportion of 0.200 in 1975; b) the artifact may be due to a change in diagnostic procedures where the diagnoses were applied more restrictively in later years (perhaps based only on medical tests rather than on symptoms).

Reporting reasons. Examples include a) a change in the tendency to have medical terminations (the company might discourage these to avoid workers' compensation insurance rate increases and the workers might wish to avoid being labeled as a "medical termination") or b) with the economic recession of the late 1970's, workers had less options for other jobs and would be more likely to hide their medical problems for fear of losing the job they had. It is important for the investigator to consider whether broader social and other factors may influence the reporting of health events over time.

Biological reasons. After eliminating the above reasons, the investigator should identify possible biological reasons for the apparent trend. Examples include a) exposures decreased over time leading to a decrease in adverse health outcomes; b) a survivor effect is occurring as the worker population stabilizes and the susceptible employees have already been terminated; and c) the newly hired employees with the substantial expansion in the mid-1970's have not been exposed long enough to develop the health problems.

Answer 5

The TWA air concentrations of platinum salts for the four days of sampling are shown below:

28 Jun 1977 -

$$\frac{11.5*(0.85) + 2.3*(1.57) + 3.5*(1.83)}{0.85 + 1.57 + 1.83} = 4.66 \text{ ug/m}^3$$

4 Aug 1977 -

$$\frac{5.0*(0.92) + 25.0*(1.63) + 120.0*(1.00)}{0.92 + 1.63 + 1.00} = 46.58 \text{ ug/m}^3$$

$$\text{11 Oct 1977} - \frac{34.0x(4.65)}{4.65} = 34.0 \text{ ug/m}^3$$

$$\text{13 Sep 1977} - \frac{1.6x(1.58) + 0.8x(4.00)}{1.58 + 4.00} = 1.03 \text{ ug/m}^3$$

Answer 5

a) Assumptions in the use of the TWA formula include the following:

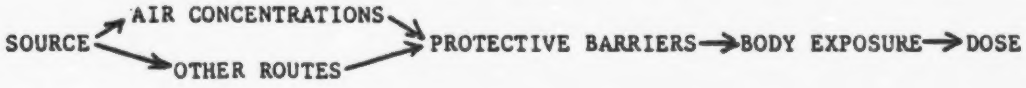
1) The samples obtained are representative of exposure levels.

2) The most relevant indicator of exposure is the average air concentration rather than short-term or peak exposures.

3) A more technical assumption is that the numerical average is the appropriate method to express average exposure. In fact, air concentrations tend to vary in a log-normal (rather than normal) distribution. Thus the geometric mean may be a better summary measure of average exposure.

b) Yes, three of the four TWA's are substantially above the levels cited in the literature (see Part I) as causing allergic health problems. The investigator should use existing literature and occupational health regulations to evaluate whether exposures appear to be excessive. (The US OSHA standard is 2.0 ug/m^3.)

To assess actual exposure, the investigator should consider the chain of transmission of the agent to the worker. For an industrial exposure, the chain may be shown as the following:



Issues to consider based on this model include the following:

1) Local ventilation and other control technology may reduce the air exposure to the worker. Measuring air concentrations with personal sampling devices is preferable to area measurements.

2) The investigator must evaluate the potential for exposure via direct contact and other routes that are not reflected in the measurement of air concentrations. Related factors include personal hygiene, eating and smoking practices.

3) The use of protective barriers, including personal protective equipment, must be evaluated in order to determine actual body exposure.

Answer 6

The medical testing procedures prior to 1979 were inadequate in that they did not include specific testing for atopic status or allergy to platinum salts. In 1979, such tests were implemented. This change in procedures must be considered by the investigator for the following reasons:

a) The change in procedures could introduce artifacts in the identification and recording of medical problems.

b) Prior to 1979, data on allergic status was not obtained; thus, no pre-exposure (baseline) health data is available for the exposed workers.

c) To the extent that atopic tendency is a risk factor for platinum salts allergy, the screening procedures implemented in 1979 should have resulted in a less susceptible population. Thus, the incidence of allergy may decrease even without any reduction in exposure.

d) The procedures for referral of workers with complaints to local medical practitioners for skin prick testing and possible medical termination are likely to have inhibited workers from utilizing the nurses station. Such procedures would bias the apparent incidence of allergy downwards.

Answer 7

The investigators asked all current employees to participate in the medical evaluation. The advantages of such an approach include the following:

a) Transfer of positions within the facility is possible; therefore, the investigators should assess the exposure histories and health status of employees who now work in nonexposed areas, but may have worked in operating areas previously.

b) Truly nonexposed employees may serve as an internal comparison group.

c) The three ways of sampling subjects in cross-sectional studies are 1) exposure-selective (select exposed and nonexposed groups); 2) outcome selective (select "cases" and a well comparison group); and nonselective or ambidirectional (select the whole population or a representative random sample). By examining all employees or a random sample of employees, the investigators are more likely to avoid selection bias. Also there is less need to decide a priori on definitions of "exposed" or "case".

d) In small facilities, it may be necessary to offer the medical testing to all employees to avoid alienating workers at the facility who may not be included. Such an approach is likely to increase participation by all employees.

Because of the high turnover rate, the investigators also decided to attempt to study all workers who had been medically terminated from the facility. Such an approach allows one to evaluate whether they had continuing health problems and whether they differed from workers still at the facility (e.g., in atopic status or other possible risk factors).

Answer 8

The key factor in field testing for occupational asthma is that the tests must be safe and feasible to conduct at the industrial facility. The most definitive test for allergic asthma is the inhalation challenge test; however, this test must be conducted in a clinical setting. Tests which may be used in the field include:

a) Questionnaire to assess symptoms, medical problems, medications, personal and family histories of allergy, full occupational history, and work history and exposures at the facility.

b) Physical examination for dermatitis, wheezing or other respiratory signs. The physical examination is not very valuable for occupational asthma.

c) Pulmonary function tests for signs of obstructive airways disease. A baseline test should be done before a workshift, if possible, after at least two days since the last workshift. This test provides an indication of fixed obstruction. The tests should be repeated after the workshift on the same day with the same testing equipment to evaluate whether exposure has induced airway obstruction. In general, the pre- to post-shift change in lung function is a specific, but not a sensitive test of occupational asthma. The lack of sensitivity is due to the fact that sufficient exposure may not occur on the particular testing day.

d) Pulmonary function tests for signs of hyperreactive airways. Recently, investigators have tended to include pulmonary challenge testing with either methacholine (a drug) or cold-air in the field evaluation of occupational asthma. Both tests can be done at an industrial facility. The subject completes a baseline lung function test and then is administered the challenge substance according to a protocol. The lung function test is repeated after the challenge. A positive test indicates the presence of hyperreactive airways, a sign of of asthma.

e) For an evaluation of a substance felt to be capable of causing allergic asthma, testing should include immunological tests, such as skin testing or possibly blood drawing for testing of specific allergic antibodies (IgE) using the radioallergosorbent test (RAST) or other techniques. Such tests can indicate the presence of IgE, but they do not prove that the asthma is due to the substance.

Each of these tests was included in this evaluation.

PART 3

Answer 9

Medically terminated workers were traced through the use of telephone books, driver license records, and word of mouth among current employees and neighbors at last known addresses. Tracing living ex-employees to participate in a medical evaluation requires different methods than the approach when doing a mortality study. The time is shorter since last employment; the investigator actually needs to contact the person and not just obtain vital records; and the search area is limited since the subject must be close enough to the facility to allow participation in the study.

Answer 10

Key concerns of workers that affect participation include confidentiality of test results, individual notification and interpretation of results, possible use of results by the management to terminate workers, nature and risks of medical tests, and amount of time or disruption in the workshift to complete the tests. Strategies should include the following:

a) Meeting with management, union and workers to educate them about the purpose and procedures of the evaluation. Encourage both management and the union to circulate a notice endorsing the medical evaluation. Posters can be posted advertising the oncoming testing.

b) Group meeting with the employees to explain the purpose and procedure of each test and to answer questions. Each of the concerns listed above should be addressed.

c) Key persons within the facility should be encouraged to personally participate in the evaluation. In this case, all top management and union leaders personally participated in the evaluation on the first day of testing.

Answer 11

When there are insufficient resources to establish a referent population, the investigators should attempt to use standardized testing procedures with established "normals". In this case, the investigators used the American Thoracic Society respiratory questionnaires modified with questions specifically on asthma symptoms as developed by well recognized asthma researchers. Pulmonary function tests and other immunology tests are well standardized.

For the cold-air challenge tests (which at the time was not as well known), the investigators did select and test a comparison group of workers. In addition, the investigators established an internal standard for test by using the results of workers who had absolutely no respiratory symptoms and were negative on all other tests of allergy. The test values of this subgroup compared very well with the few published reports for results on normal populations.

PART 4

Answer 12

(Note: the point of these questions is to encourage the students to identify possible sources of bias in conducting epidemiological studies. The answers are provided as examples and are not the only possible answers.)

It should be noted that the participation of 29 of 36 terminated workers who were located was a reasonably good participation rate. In any case, the investigators must consider whether the loss-to follow up (the 13 terminated wokers who could not be located) and the nonparticipants (the seven who declined to participate) could be different than the ones who did participate in the study. Possibilities include that the lost persons could have died due their illnesses or may have moved to another climate because of illness. They also could have recovered and moved elsewhere for new employment. The persons who declined to participate are more likely to be less ill or less concerned about their illness than ones who elected to participate. Thus the participants would tend to increased the apparent prevalence of problems.

One may evaluate the potential for bias by a) reviewing the personnel and medical records of the terminated employees to evaluate whether the participants differed systematically from the non-participants and loss-to follow-up workers, and b) administering a brief questionnaire (even over the phone) to the nonparticipants to provide some data on their health status since leaving the facility.

Answer 13

The nine current workers unavailable at the time of the study fall into two groups. The persons on vacation are unlikely to be substantially different than the workers at the facility. On the other hand, workers who are unavailable because they are ill, may be ill due to exposure. It is important to determine why each absent employee is ill.The 16 current workers who declined to participate are probably different than those who do participate. In many instances, older or long-term employees are less likely to participate. Unlike with the terminated workers, some current employees may decline to participate, if they believe they are affected and that participating in the study may lead to their termination. It is critical for the investigators to insure the confidentiality of test results. The potential bias introduced by the nonparticipation may be estimated by comparing the personnel records and demographic data for participants and nonparticipants. During analysis, it is valuable to make several calculations of the measures of effect making different assumptions (best case, likely case, and worse case situations) as to the effect of the nonparticipation. These alternative results provide an indication of range of possible bias.

Answer 14

As with the above questions about interpreting outcomes, the students must consider the possibility that the result is either artifact or real. The results may appear to be different if the tests were done in a different way by the investigators, if earlier reports were incorrect, or if the exposures actually involved different platinum salts.

Biological reasons for the difference in results include that the persons included in the study had been terminated only a short period of time and, thus, their tests had not returned to normal yet (actually not the case since some had not worked at the facility for several years); there was higher exposure at the facility; because of inadequate pre-employment screening, the facility had exposed susceptible persons who may have remained ill longer; and due to the lack of periodic screening, the employees continued to be exposed to the platinum salts for substantial periods after becoming sensitized. Such continued exposure can cause an increase in allergic antibody levels.

PART 5

Answer 15

The prevalence odds ratio is the appropriate measure of effect when the investigators are using a prevalence study to estimate the relative risk (rate ratio) of a chronic condition, assuming that the incidence of disease and exposure are stable (i.e., steady-state condition). The prevalence ratio is the appropriate measure of effect, when the investigators are using the prevalence study to estimate the relative risk (attack rate ratio or cumulative incidence ratio) of an acute problem or epidemic, assuming that the period of risk essentially has passed and that the population at the time of the study is nearly equal to the population at the beginning of the epidemic (i.e., the "rare disease" assumption).

The prevalence odds ratio was used in this study because the investigation concerned the development of occupational asthma due to chronic, on-going exposures.

(Note: Additional information for the instructor on the use of the prevalence odds ratio and the prevalence ratio is provided below (see also Kleinbaum, et al. 1982). The students should not be expected to learn the material in this depth.)

- -

Further comments on the use of prevalence odds ratios and prevalence ratios

By definition, $P/(1-P) = ID \times D$ where P is the prevalence proportion, ID is the incidence density (person-time incidence), and D is the average duration of the health condition.

To estimate relative risk in two subpopulations of exposed (e) and nonexposed (o), one could divide the above formula for the two groups:

$$\frac{P_e/(1-P_e)}{P_o/(1-P_o)} = \frac{ID_e \times D_e}{ID_o \times D_o}$$

The left side of the equation is the prevalence odds ratio (POR), and the right side of the equation is the rate ratio (RR) times the ratio of the average duration of disease in the exposed by the unexposed. Thus,

$$POR = RR \times D_e/D_o.$$

Since the rate ratio is the appropriate measure of effect for a chronic condition, the prevalence odds ratio is the best estimate of the rate ratio in a prevalence study. Note that the estimate depends upon the assumption of equal duration. Since illness due to exposure may cause workers to leave work (as with allergy due to platinum salts) prematurely, it is likely that the disease duration in the study population will be shorter for the exposed and, thus, the POR will tend to underestimate the rate ratio (i.e., be a conservative estimate of the relative risk).

On the other hand, for an acute outbreak or epidemic, the appropriate measure of effect is the relative risk of attack among the exposed compared to the nonexposed (i.e., the attack rate ratio - well known in infectious disease epidemiology). For exposed and non-exposed, the formula would be as follows:

$$\text{Attack Rate Ratio (AR)} = \frac{C_e/N_e}{C_o/N_o}$$

where C is the number of cases and N is the population at the beginning of the period of risk.

By assuming that essentially no one has withdrawn from the population, then C becomes equivalent to the prevalent cases and N becomes equivalent to the population number. Thus the attack rate ratio becomes equal to the prevalence ratio. In other words, the prevalence ratio is the appropriate estimate of the relative risk for an acute (epidemic-like) problem.

It should be noted that the prevalence odds ratio has some advantages over the prevalence ratio, in addition to the above issues: a) the POR can be calculated in all three methods of selection study subjects (i.e., exposure-selective, outcome-selective, and non-selective) while the PR can be calculation only for exposure-selective and non-selective sampling schemes; b) the POR as a cross-product ratio is more stable as a measure of effect than the PR in the face of varying underlying prevalences. For very small prevalences among the unexposed the PR becomes quite unstable.

Answer 16

The prevalence odds ratios for each health outcome among platinum salts skin test positive versus negative current workers are shown below:

Rhinitis -	13	28	14
	2	64	66
	15	92	107

$$\text{POR} = \frac{13 \times 64}{2 \times 28} = 14.86$$

Asthma symptoms - 3.26
Reported dermatitis - 4.42
Cold-air challenge - 6.58
Elevated IgE - 4.16

Note that atopic status and smoking are not health outcomes of platinum salts sensitivity and should not have been included by the students in this question.

Based on the odds ratios, platinum salts sensitivity is an apparent risk factor for each health outcome. To confirm this impression, the investigator could calculate the Chi-square test statistic and derive 95% confidence intervals for the odds ratio. Use of these formulas is not included in this exercise.

Answer 17

Interpretation of a risk factor requires an a priori understanding or belief in the directionality of an observed association between two factors. Specifically, it is plausible to assume that platinum salts sensitivity may have caused the above health outcomes. However, it would not have determined atopic status and past smoking history and thus, could not be a risk factor for these conditions. On the other hand, it is plausible that an atopic tendency or smoking could increase the risk of platinum salts sensitivity (both have been reported in the literature to do so in other instances of occupational asthma).

a) Smoking appears to be a strong risk factor for platinum salts sensitivity. Only 34% of current workers who were platinum salts skin-test negative were current smokers, compared to 80% in current workers who were skin test positive and 70% in the terminated workers. These differences are highly significant with statistical tests.

b) It is very difficult to determine whether an atopic status is a risk factor for platinum salts sensitivity. The proportion of persons who are atopic positive in each of the three groups of study subjects is approximately equal. The differences are not statistically significant.

On the other hand, several points must be made to suggest that one should consider it a risk factor: a) reports in the literature have reported that atopic status is a risk factor for platinum salts allergy; b) in comparing the two current worker groups, the positive skin test workers do have a higher proportion of atopic positive subjects (40% versus 32%). The difference is not statistically significant but the size of the study population is small and, thus, the power of the study is weak. With a larger study population this difference would have been statistically significant; c) the lower proportion of atopics in the terminated group could be a manifestation of the bias due to loss to follow-up and should not be considered too strongly in interpreting the overall effect of atopic status.

Overall, one would conclude that atopic status is not a clear risk factor for platinum salts in this particular study; however, the limitations of the study (i.e., cross-sectional study with less than 100% participation and no definitive bronchial challenge testing) preclude making a definite conclusion on this issue.

c) Clearly smoking, and possibly atopic status, are independent risk factors for platinum salts sensitivity. They also are risk factors for most of the health outcomes. Therefore, they are potential confounders in the apparent association between platinum salts sensitivity and the health outcomes. To evaluate the role of smoking and atopic status, the investigator would stratify on these variables in analysing the association between platinum salts sensitivity and the health outcomes.

Answer 18

To the extent that persons with true platinum salts allergy who had adverse health outcomes were misclassified as being platinum salts skin test negative, the association between allergy and the health outcomes would be weakened. In other words, misclassification due to lack of sensitivity would tend to underestimate the effect of platinum salts allergy.

Answer 19

a) The time of onset of the asthma symptoms strongly influences the apparent association between platinum salts skin test result and asthma symptoms. As calculated in question 16 from the data in Table XLIX, the odds ratio for asthma symptoms is as follows:

POR = (9 x 63)/(6 x 29) = 3.26

However, the persons that had an onset of asthma before being hired had a platinum sensitivity comparable to those with no symptoms, while workers with symptoms onset after hiring had a much higher proportion of persons with a positive skin test. Excluding the 18 persons with onset before hiring (since they actually were not at risk of having an onset after hire), the odds ratio for new asthma symptoms is as follows:

POR = (8 x 63)/(6 x 12) = 7.00

Clearly, by eliminating the workers who had symptoms not necessarily due to exposure, the strength of the association between the skin test and asthma symptoms is much greater.

b) As was done in 19a above, one could eliminate the persons, who are not at risk of developing symptoms after hiring, because they already had symptoms before being hired. At the same time, this group should be closely examined to see if the severity of their symptoms and other health outcomes is different, because they may, in fact, be a group with greater susceptibility to adverse health outcomes.

Answer 20

The inclusion of the medically terminated group allows the investigators to interpret the effect of personal risk factors such as smoking and atopic status, as discussed above. These seem to demonstrate that the findings among the current workers are not merely spurious due to a survivor effect.

A hypothetical example of a survivor effect would be, if the prevalence of smoking among the terminated workers had been like that of the negative current workers. One could than have concluded that, in contrast to the actual findings, smoking was protective and allowed sensitized workers to remain at the facility longer.

The inclusion of the terminated workers also allows the investigators to find out more about the natural history of the disease after exposure has ceased. In this case, symptoms tended to return to nearly the prevalence among the negative skin test current workers, but airway hyperreactivity and elevated IgE remained. Thus, these terminated workers remained at high risk of developing asthma if exposed to new agents.

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R

PESTICIDE POISONING AMONG ANTIMALARIA WORKERS*

PART 1

You are the medical officer in charge of the malaria control programme in Pakistan (Baker, *et al*, 1978) You have learned of cases of pesticide intoxication beginning in late June within weeks of the beginning of that season's spraying. That season malathion had replaced DDT which was used previously but abandoned as the mosquito vector was found to have developed resistance to the insecticide. Malathion was selected in part on the basis of it being one of the safest insecticides as confirmed by the field testing of malathion in Nigeria (Elliott & Barnes, 1963), Uganda (Najera, *et al*. 1967), and Central America (WHO, 1967) which had demonstrated little evidence of human toxicity.

There were 77000 workers (working as 1100 spray teams) employed by the malaria control programme in the Punjab and the Northwest Frontier Province, the main areas of malathion usage. Each spray team consisted of five spraymen, one mixer, and one supervisor. The signs and symptoms of the illness were suggestive of an organophosphorous insecticide intoxication. Little else was known except that the illness appeared more common on Friday and Saturday than on Sunday. Also five deaths had been attributed to pesticide poisoning including two mixers and three spraymen. Clinically it appeared that the illness was more severe among those using either of two Italian brands of malathion. Three deaths had been reported among those using these Italian brands and two deaths had occurred in an area using an American brand.

Question 1
How would you proceed to investigate this situation?

Question 2
State the main problem in the episode described.

Question 3
In your opinion what preliminary organizational network should you establish to investigate this epidemic?

Question 4
What are the likely symptoms and signs you would expect in a case of acute malathion (organophosphorous compound) poisoning? What combination of symptoms would you use for a case definition?

Question 5
What are the possible reasons as to why symptoms appeared on Friday/Saturday, while the workers were symptom-free on Sunday?

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*By J. Jeyaratnam 1985; revised December 1985.

Question 6

What could be the possible reasons as to why malathion (known to be a safe pesticide) should result in an outbreak of poisoning among workers?

PART 2

Cases of organophosphate poisoning have now been confirmed by medical personnel both on the basis of clinical examination and by documentation of depressed cholinesterase levels. To define the extent of the epidemic and to explain why disease was occurring with a relatively safe insecticide, you have planned a questionnaire survey. It is necessary to define a case for the questionnaire survey. An episode of acute intoxication was defined as a team member having any four of the following five symptoms: blurred vision, giddiness, nausea, vomiting or abdominal pain. The incidence of intoxication was determined by interviewing a random sample (approximately 10%) of the spraymen, mixers and supervisors in Punjab and Northwest Frontier Province. Questionnaires were administered to 425 spraymen, 86 mixers and 95 supervisors, a response rate of 72.1% of those selected for interviews. The number of persons with at least one episode of acute malathion intoxication is shown in Table L.

Table L Incidence of acute malathion intoxication among malaria control workers, interviewed during 1976, Pakistan

Type of work	Number interviewed	Number with at least one episode of poisoning (%)
Spraymen	425	174 (41)
Mixers	86	33 (38)
Supervisors	95	19 (20)

Source: Baker, et al. 1978, page 31, modified.

As the total numbers of spraymen, mixers and supervisors employed in the malaria control programme were known, it was possible to estimate on the basis of the above incidence that there were a total of 2810 workers with at least one episode of pesticide intoxication in July 1976.

Question 7

What type of epidemiological study was this interview survey?

Question 8

What are your comments on:

a) sampling methods?
b) response rate of 72.1%?

Question 9

How would you now proceed?

PART 3

It was now evident that an extensive outbreak of acute malathion poisoning was occurring among workers in the malaria control programme. Among the three categories of workers, spraymen and mixers were observed to have the highest prevalence of symptoms. The major concern at this stage was to identify possible causes as to why malathion, a usually safe pesticide, should have resulted in such an extensive outbreak of poisoning among users.

For this the staff from the provincial and district malaria programmes observed spray teams during a typical working day and completed a detailed work practice and symptom checklist on each worker. Improper work practices, such as sprayers working in clothes wet from pesticides, were observed. Further these same clothes were worn for several days without washing. Both spraymen and mixers had extensive skin contact with pesticide during the filling and pressuring of the spray tanks. Some mixers mixed the malathion suspension with their hands. Many spray cans leaked pesticide onto the arms, hands and chests of spraymen. When spray nozzles became clogged, the spraymen sometimes blew through them to unclog them.

Question 10

How would you attempt to establish the fact that poor work practices, as observed, were likely to have resulted in this outbreak of malathion intoxication or are you satisfied with the description of the work practices? Would you want to further characterize the work practices ? If yes, how?

PART 4

Table LI presents the results of a skin patch survey of workers in three jobs, spraymen, mixers, and supervisors, from three body sites. In addition, air samples were taken. Airborne exposure of sprayers was very low, 3% of the US exposure standard.

Table LI Malathion concentration in skin-patch samples by job and body surface, Pakistan 1976

	Mean exposure (ug/cm^2) at each site								
	Forehead			Chest			Arm		
Job	No.	Mean	Range	No.	Mean	Range	No.	Mean	Range
Spraymen	19	39.3	6.7–202.5	19	13.6	1.4–105.0	18	41.5	2.9–88.2
Mixer	1	5.9	-	1	1.3	-	1	49.6	-
Supervisor	3	2.2	1.6- 2.9	3	0.9	0.5- 1.5	2	2.9	2.8, 3.0

Source: Baker, et al. 1978, p. 34; cited in WHO/TRS 667, 1982, p. 27.

Question 11

Is this data consistent with the observation of work practices described in part 3?

Question 12

Which is the important route of exposure, respiratory or dermal?

Question 13

Are you satisfied that poor work practices represents an adequate explanation for this epidemic? If not please restate any additional hypothesis and describe how you would proceed with an investigation to evaluate your theory.

PART 5

You conclude that while work practices are poor, that they would not alone explain the outbreak of illness. From the questionnaire data you also have confirmed higher prevalence rates in workers using the Italian brands, but because teams have used all brands from time to time, you decide to do a small survey of cholinesterase depression in order to correlate effects with current pesticide exposure. Table LII presents cholinesterase depression data by job and brand of insecticide. Brand 2 and 3 are of Italian origin.

Table LII End-of-day red-cell cholinesterase activities and mean relative changes* by job category and type of pesticide used, Pakistan (1976)

	Cholinesterase activities pH/h**											
	Supervisor			Mixer			Spraymen			Relative change		
Pesticide	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	Supervisor	Mixer	Spraymen
Brand 1	14	0.62	0.20	11	0.58	0.10	66	0.58	0.12	+ 5.9	- 0.8	- 3.1
Brand 2	2	0.59	0.00	4	0.34	0.06	18	0.38	0.14	+ 3.2	-20.1	- 11.2
Brand 3	6	0.59	0.17	6	0.39	0.25	28	0.24	0.15	+ 0.2	-39.2	- 46.7

* (Evening red-cell cholinesterase activity minus morning red-cell cholinesterase activity)/Morning cholinesterase activity.

** Normal range: 0.53-0.93 pH/h, based on testing of unexposed male Pakistan villagers.

Source: Baker, et al. 1978, p.32.

Question 14

Which brand do you think is responsible for the epidemic?

Question 15

Please suggest some hypothesis for the differences observed between brands.

Conclusion

Table LIII presents chemical data on the malathion content and degredation products of the three brands. The clearest difference is in the content of isomalathion, although differences in minor constituents such as trimethyl phosphorodithioate are observed as well. The authors postulated that different chemical carriers used in the implicated brands may have precipitated the formation of degradation products.

Question 16

What programmes would you have initiated to reduce the possibility of a continuation of this epidemic?

Table LIII Percentage of malathion and degradation products in samples from three suppliers used in Pakistan 1976

Code	Chemical name	Mean in: Brand 1 (N=14)	Mean in: Brand 2 (N = 4)	Mean in: Brand 3 (N = 6)
D.M.P.M.	O,O-dimethyl phosphonothioic acid	-	0.6	-
T.M.T.P.	O,O,O-trimethyl phosphorodithioate	0.2	0.1	0.5
T.M.E.	O,O,S-trimethyl phosphorodithioate	0.9	0.5	1.0
D.E.P.	Diethyl fumarate	0.6	0.6	0.5
D.E.M.S.	Diethyl mercaptosuccinate	0.3	0.3	1.2
D.E.M.M.S.	Diethyl amethylmercaptosuccinate	0.3	0.3	0.4
P.S.P.	Tetramethyl thiopyrophosphate	0.8	0.2	2.0
Mixed ester	O,O-dimethyl S-(1-carbomethoxy, 2-carbomethoxy) ethyl phosphorodithioate		0.2	2.6
2.3				
Malathion	O,O-dimethyl S-(1,2-dicarbethoxy) ethyl phosphorodithioate	44.1	45.5	35.3
Maloxon	O,O-dimethyl S-(1,2-dicarbethoxy) ethyl phosphorodithioate	0.01	-	0.1
Isomalathion	O,S-dimethyl S-(1,2-dicarbethoxy) ethyl phosphorodithioate	0.3	2.1	3.1
T.E.M.S.	Tetracthyl thiodisuccinate	0.9	0.1	0.2
T.E.D.S.	Tetracthyl dithiodisuccinate	0.7	0.1	0.6

INSTRUCTOR'S NOTES

PESTICIDE POISONING AMONG ANTIMALARIA WORKERS

Summary

In 1976, an epidemic of organophosphate insecticide poisoning due to malathion occurred among 7500 field workers in the Pakistan malaria control programme. In July, the peak month of the epidemic, it was estimated that there were about 2800 cases. In field studies low red cell cholinesterase activities were associated with the signs and symptoms of organophosphate insecticide intoxication.

Toxicity was seen with three different formulations of the insecticide and was greatest with the products containing increased amounts of isomalathion, a toxic malathion degradation product. Poor work practices, which had developed when DDT was the primary insecticide for malaria control, resulted in excessive skin contact with and percutaneous absorption of the pesticide. Airborne malathion concentrations were very low. Implementation of good work practices and proscription of use of the two pesticide formulations most contaminated with isomalathion halted the epidemic in September 1976. An extensive training programme and surveillance system for pesticide toxicity preceded the 1977 spraying operation.

The purposes of this teaching exercise are:

1) To introduce concepts of the cross-sectional and related study designs.

2) To demonstrate the orderly steps useful in investigation of an acute noninfectious disease outbreak.

3) To demonstrate the need and approaches to exposure assessment.

4) To demonstrate that the first explanation (poor work practices) does not explain the observed facts (a safe pesticide causing an epidemic) and that a plausible explanation must be sought to explain the observed facts.

PART 1

Answer 1

An approach to the procedure for investigating an epidemic should include the following steps (Lowe & Kostrzewski, 1973):

a) establish the existence of an outbreak (epidemic);
b) verify the diagnosis;
c) quickly search for all existing cases;
d) describe and analyse cases according to time, place and person;
e) formulate hypotheses;
f) plan a study to test all reasonable hypotheses;
g) conduct the study and analyse findings; and
h) recommend control measures.

Answer 2

Malathion, an organophosphorous insecticide previously demonstrated to be extremely safe, has been observed to cause unexpected episodes of poisoning resulting in at least five deaths. The problem is both serious and unusual, hence requiring further investigation.

Answer 3

The study population is large and it is possible that Pakistan, like many other developing countries, may not have the resources (finances, manpower and equipment) to undertake the organization and execution of the study alone. Also given the implications of this epidemic for public health in other countries conducting similar programs with malathion, it is advisable to have an outside independent body associated with the study. In this instance the study was undertaken in collaboration with the WHO and the Centers for Disease Control, Atlanta, USA.

Answer 4

The clinical signs and symptoms of malathion poisoning are induced by inhibition of the enzyme cholinesterase (ChE). The earliest symptoms are usually blurred vision, headache, dizziness, nausea and vomiting, followed by abdominal pain, sweating, miosis, salivation, lacrimation, bronchial secretion, muscular weakness, tremor of the extremities, fasiculations, difficulties in breathing, paralytic signs and ataxia. Several clinical classes of malathion poisoning have been described by WHO (WHO, 1982) (Table LIV) which states that in acute poisoning with organophosphorous compounds, the clinical manifestations generally appear after inhibition of more than 50% of the serum cholinesterase, and the severity of manifestations parallels the degree of serum ChE activity: there is up to 20-50% inhibition of ChE level from the baseline level in mild poisoning; in moderate poisoning the serum cholinesterase activity is 10-20% of normal value and it is less than 10% of normal value in severe poisoning.

Table LIV Clinical classes of malathion poisoning

Class and type		Criteria
1	Clinically insignificant exposure	No significant signs or symptoms. Vital signs normal. Physical examination negative. History of minimal exposure, usually no odor of malathion.
2	Mild non-specific clinical symptom	Nausea, vomiting, dizziness, malathion odor detected.
3	Mild to moderately severe specific clinical symptoms	Sialorrhoea, few rales or ronchi, pupils small, conscious, sometimes deep harsh breathing, glycosuria not infrequent.
4	Severe specific clinical symptoms	As above but more marked, including hypotension, Cheyne-Stokes respiration, incontinence, coma, cyanosis, loss of reflexes, fasiculations and convulsions.

It is important to stress the need to define a case of poisoning for the purposes of the investigation. The typical dilemma is between a too rigorous case definition which leads to misclassification of some of the poisoned into the non-case group, and too lenient a definition which leads to the opposite problem.

Answer 5

The employees work a six-day week with Sunday being an off-day. The main reason as to why symptoms appear towards the end of the work-week is because of the cumulative depression of the ChE level due to the repeated daily exposure to malathion. The symptoms appear when ChE level is significantly depressed. As ChE is rapidly regenerated when exposure is discontinued, no symptoms are evident on Sunday.

Answer 6

There are obviously a large number of possibilities:

i) Knowledgeable use of wrong concentration of malathion. Such a possibility is unlikely as studies in other developing countries (Jeyaratnam, 1980) have indicated that government employees in vector control programmes, unless very closely supervised, are known to use concentrations lower than that recommended. This is done deliberately by the spraymen both to reduce a possible hazard to themselves as well as possibly to make some profit from the unutilized pesticides. Whereas the situation is quite different among owner farmers who tend to use pesticide concentrations far in excess of that recommended (Jeyaratnam, 1982) so as to ensure effective protection of their crops against pests.

ii) The possibility of grossly improper and unsafe work practices must be considered.

iii) Some hitherto undetected factor - this must be given serious consideration because of the prior safe use of malathion in antimalaria control programmes.

PART 2

Answer 7

Of the three major types of epidemiological study, cohort, case-control, and cross-sectional, this study has attributes of two, cross-sectional and cohort. Characteristically in a cross-sectional study, a population is questioned and sometimes examined for evidence of current disease, and current or past exposure. In this instance, workers were asked about current and past episodes of illness. Since malathion poisoning would be of relatively short duration, it would be more likely that participants would have had past episodes than would be ill at the time of the questionnaire survey. This study has some attributes of a cohort study, in that all participants are asked about exposure and only the first episode of illness per worker is counted as a case. Unlike a cohort study however, some cases of poisoning will not be included in the survey either because they are too sick to be available for the survey, or like the five, they will have already died. Technically, this study is called a "backward prevalence study." This type of study is used as an inexpensive substitute for a cohort study for acute diseases. In a cohort study, all participants, including survivors and decadents would be characterized as ill or not ill.

Later on the students will be asked to identify the study type when the researchers question the participants and do a cholinesterase determination on each. Since participants are being asked about exposure and tested at the same time, this would be an example of a cross-sectional study. More important that being able to correctly name the study type, is a recognition of the potential bias introduced, for example, if only survivors are included in the "backward prevalence study." In its guidelines on studies in environmental epidemiology (UNEP/ILO/WHO, 1983), WHO has identified the different types of epidemiological studies as have Kleinbaum and coworkers (1982)

Answer 8

a) A simple random design was used to select a sample. But no information was available on the distribution of workers in the Punjab and the Northwest Frontier Province. If the numbers were very different in the two provinces, different and unequal sampling ratios may have been appropriate to insure an adequate sample size in each area.

b) A response rate of 72.1% is reasonably adequate but one would have expected a higher rate from regular government employees. Further there was no information given about the response rate among different categories of workers, i.e. spraymen, mixers and supervisors. An attempt should have been made to study a small sample of non-responders. When this was done, it was observed that some of the non-responders were those who were ill during the episode and had given up employment. Thus the rates provided were underestimate.

Answer 9

To this point the existence of an epidemic has been confirmed and the greater rate demonstrated of disease in the spraymen and mixers as compared to the supervisors. Previously it has been stated that some hypotheses should now be tested in studies. These include poor work practices, and some chemical alteration in the pesticide.

PART 3
Answer 10

It would be appropriate in view of the nature of the improper work practices to estimate the extent of dermal exposure to examine its relationship to cholinesterase activity. Further it would also be necessary to examine the extent of occupational exposure from airborne malathion.

The dermal absorption was assessed by a modification of the method of Durham and Wolfe (1962) to evaluate dermal absorption of malathion. It was observed that exposure to skin surfaces varied with the job category: spraymen had the highest exposure to forehead and chest; the mixers had the highest exposure to arms; supervisors had the lowest exposures (Table LI).

PART 4

Answer 11

Workers with the greatest dermal exposure to malathion (spraymen and mixers) (Table LI), were more severely affected than supervisors. Dermal absorption, which resulted from excessive skin contact during spraying and mixing operations, was the primary route of pesticide uptake; respiratory exposure was relatively unimportant.

Answer 12

Air samples were obtained by standard methods to assess respiratory exposure from airborne malathion. Exposure of spraymen to airborne particulate matter and vapours was extremely low (mean 0.43 mg/m^3) (NIOSH, 1976), less than 3% of the recommended US standard for occupational exposure to airborne malathion (15 mg/m^3 measured as an 8-hour time-weighted average when skin exposure is prevented) (NIOSH, 1976). Peak airborne exposures were only slightly higher (mean 1.54 mg/m^3). Airborne concentrations of brands 1 and 3 were not significantly different.

Answer 13

It has now been demonstrated by observation and more quantitatively that spraymen and mixers had substantially more dermal exposure than supervisors. It has not been explained why malathion, a "safe" pesticide was causing this outbreak. Nor has the observation been discussed that two of the brands were associated with more common and severe symptoms.

The best way to demonstrate a relationship between a particular brand of malathion and toxicity would be to measure cholinesterase levels. The greater the depression of cholinesterase levels, the greater the toxicity of a particular brand of malathion. Similarly cholinesterase estimations among the various categories of workers would indicate the category of workers affected. The cholinesterase analyses were performed in the laboratory by a modification of the standard method of Michel (1949).

Part 5

Answer 14

Sprayers and mixers who used brand-3 malathion had the most severely depressed red-cell cholinesterase activities (Table LI); the average decrease over a single working day was 40-45%. Cholinesterase depression with brand 2 was significantly greater than with brand 1 (t=5.97, p 0.01, and brand 3 caused significantly more depression of cholinesterase than brand 2 (t=3.10, p 0.01). Supervisors had cholinesterase activities which were slightly reduced but which were significantly higher than those in mixers and spraymen using brands 2 and 3 (p 0.01).

Answer 15

The two malathion preparations imported from Italy were found to cause more toxicity than the preparation imported from America. Further brand 3 is seen to be the most toxic of the three brands of malathion used.

The three brands of malathion need to be analysed to determine their constituents in searching for the factors contributing to the increased toxicity of malathion. The samples of malathion were collected and analysed at the Centers for Disease Control, Atlanta, USA. The concentrations of malathion and twelve minor components in the powders were determined by gas liquid chromatography.

Brand 3 contained the lowest concentrations of malathion and the highest concentrations of four malathion breakdown products: isomalathion, methyl thiopyrophosphate (PSP), diethyl mercaptosuccinate (DEMS), and trimethyl phosphorodithioate (TME). The *in vivo* toxicity of the pesticide samples correlated best with the isomalathion content: a highly significant linear correlation (r=0.83) was noted between the average red-cell cholinesterase activity of the team and the isomalathion content of the pesticide used by the team on the day blood samples were obtained. Samples of pesticides were administered orally to rats, at 4-6 dosage levels per sample to determine LD_{50} values. Brands 2 and 3 had significantly lower LD_{50} values (626 and 651 mg/kg, respectively, based on 50% powder) than brand 1 (1940 mg/kg).

The degradation products in the malathion preparations manufactured by the two Italian firms increased the human and animal toxicity of these products. Although the clearest statistical correlations were noted between isomalathion concentrations and toxicity measurements, other minor components such as TME, may also have contributed to the increased toxicity. Synergism between different organophosphate compounds has been demonstrated *in vitro* and may have accounted for the observed enhancement of toxicity in the Italian products. Carriers and surfactants used in the manufacture of malathion, water-dispersible powders, are probably important in the formation of isomalathion and other toxic minor components in powders held under tropical storage conditions (WHO, 1979).

Conclusion

Answer 16

At least three programmes which may forestall further outbreaks should be discussed.

a) The importance of healthful work-practices.

b) The value of a disease surveillance programme of determine the effectiveness of the programmes suggested and also the basic preventive programmes. Suppose for instance that you had ascribed the outbreak to poor work practices alone. A surveillance scheme would then detect the unexpected cases that may occur even with good work practices.

c) A practical research programme to fully understand why the Italian products were toxic, in order to change some aspect of their manufacture or handling, or to enable other imports with similar problems to be screened before they are used.

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S

CHRONIC RESPIRATORY DISEASES IN COTTON TEXTILE WORKERS*

PART 1

The Egyptian National Health Insurance System, since 1977, has had the responsibility for carrying out periodic medical examinations for all workers exposed to the hazards specified in the Egyptian Social Security Act. Byssinosis due to exposure to cotton dust is compensatable, while occupational asthma and chronic nonspecific pulmonary disease (CNSPD) are not, even though they may be work related. The System holds regular monthly meetings to review occupational disease reports from all over Egypt. Cases are subsequently referred for compensation.

The Statistics Unit of the Health Insurance System had observed that while cases of byssinosis were reported in textile and other plants processing cotton in the Delta region, no cases of byssinosis were reported in Cairo. On a countrywide basis, according to workmen's compensation records, cases claiming compensation for byssinosis were less than 0.05% of those exposed to cotton dust and in Greater Cairo there were none. The textile industry is one of the largest and oldest in Egypt. The cotton used is locally produced, long fibre, and handpicked which results in a low debris content.

Scientific reports on the prevalence of byssinosis and CNSPD have been published by several research institutions and universities in Egypt (El-Batawi, 1962; El-Batawi & Shash, 1962; El-Batawi, *et al*. 1964). The prevalence of byssinosis is reported as 10-30% among exposed workers in ginneries, carding and blowing operations and varied according to the type of cotton processed, degree of dustiness and the industrial process (El-Batawi, *et al*. 1964). On the other hand, studies carried out in other mills in Egypt have failed to reveal cases of typical byssinosis but pointed to a high prevalence of CNSPD (Abou Ali, 1975; El-Samra, 1975; Qasim, 1977; El Sokbi et al., 1982) or to cases of "atypical byssinosis".

Question 1

What role might these monthly meetings have in the prevention of occupational disease?

Question 2

Offer some plausible explanations for the differences observed between the Delta and Cairo areas.

Question 3

How would you proceed to investigate the problem?

---

* By G.H. El-Samra, 1985; revised December 1985.

PART 2

Available information

In Egypt, El-Batawi in 1962 investigated the prevalence of byssinosis in the cotton industry and found that, among 900 workers, the prevalence was: 38% in ginneries, 53% in bale pressing, and 27% in the card rooms of spinning mills. Cases were diagnosed essentially on the basis of chest tightness on the first workday of the week.

In a subsequent study, El-Batawi and Shash (1964) investigated 99 male workers in ginning and spinning mills. In this study the prevalence of byssinosis was: 33% in ginnery workers, 25% at the beginning of blowing, 10% at the end of blowing, 18% total blowing, and 43% among card room workers.

El-Sobki (1975) investigated three textile mills, where he examined 664 workers. He demonstrated a fall in the forced expiratory volume of the first second (FEV_1) at the end of the work shift in workers exposed to cotton dust. However, he did not find any clinical cases of byssinosis, which he explained as being due to the short period of exposure. He was able to demonstrate a significant relationship of cotton dust to the prevalence of chronic bronchitis among the workers examined. The same plants were surveyed again in 1981 and again a high prevalence of CNSPD and "atypical byssinosis" was observed; no cases of typical byssinosis were discovered. Atypical cases had chest tightness and shortness of breath which has no regular relation to days of the week (El-Sobki, et al. 1982). Similar results were reported by Abou Ali (1975) and Qasim (1977), who both found a high prevalence of CNSPD but not typical byssinosis.

Results of environmental investigations in all reported studies pointed to fairly dusty conditions. Dust concentrations ranged from 0.15-10 mg/m^3.

Diagnostic criteria in these studies were fairly uniform and followed those available in the current literature. These included:

- Chronic bronchitis: is diagnosed when the patient has chronic or recurrent cough together with expectoration which occurs on most days for at least three months in the year during at least two years; provided localized chronic disease, or generalized specific disease can be excluded.

- Simple bronchitis: is diagnosed when there is chronic or recurrent cough, either dry or productive of mucoid sputum for periods shorter or less frequent than those necessary for the diagnosis of chronic bronchitis.

- Bronchial asthma: is a reversible reduction in the diameter of the bronchi manifested by attacks (recurrent) of chest wheezing or dyspnoea in between which the patient is usually free of symptoms (cardiac causes being excluded). During the attack, obstructive ventilatory impairment can be demonstrated which will usually improve after the administration of bronchodilators.

- Emphysema: is diagnosed on the basis of increasing dyspnoea on exertion (cardiac causes being excluded) and a combination of several of the following signs and symptoms: limitation of chest movements, hyperinflation of the chest with transverse position of the ribs, hyperresonance, encroachment on cardiac and hepatic dullness, diminished diaphragmatic movements as shown by tidal percussion, diminished breath sounds and prolonged expiration, wheeze and varying degrees of obstructive ventilatory impairment.

- Byssinosis: is diagnosed on the basis of the characteristic symptoms of chest tightness and/or shortness of breath on returning to work after an absence (Saturday tightness) (Qasim, 1977).

The situation with byssinosis worldwide seems to parallel that of Egypt (WHO, 1983). Cases of byssinosis have been reported in cotton processing countries such as England, India, Israel, the Netherlands, Sudan, Sweden and Uganda. In other countries, however, such as USSR, Czechoslovakia and in some studies in Poland, no cases of byssinosis were detected but rather CNSPD. In Greece, lung function changes have been reported in workers exposed to cotton dust but no cases of byssinosis; similar results have also been reported in the USA (WHO, 1983).

Question 4

If you were conducting an investigation, how would you proceed?

PART 3

Three plants in the Cairo area were selected for the study. In the three, the industrial process started with raw cotton (bales) then proceeded to the finished yarn through mixing, cleaning, and carding. The various industrial processes were carried out in separate departments in the two larger plants. In the third, all work processes were carried out in one common hall.

Environmental studies

Table LV shows mean concentrations of respirable dust, ranges and number of samples taken in each department. Sampling covered mixing, carding and spinning operations in the first two plants and the common hall in the third.

TABLE LV Dust concentrations in various departments in the three textile mills (respirable dust) in mgm/m^3

Factory	Department	No. of samples	Dust concentrations range	mgm/m^3 Average
A	Mixing	6	0.75 - 1.14	0.89
	Carding	6	0.58 - 0.89	0.72
	Spinning	6	0.39 - 0.71	0.52
B	Mixing	6	0.97 - 1.17	1.05
	Carding	6	0.56 - 0.84	0.69
	Spinning	6	0.37 - 0.58	0.45
C	All	8	1.01 - 1.54	1.25

Medical Studies:

The total number of workers examined in the three plants was 2723 (1885 men and 838 women). Table LVI shows the distribution of workers according to age. The majority of workers were above 30 years of age (82.1%)

TABLE LVI Distribution of workers according to age

	Mill							
	A		B		C			
Age years	No. of workers	%	No. of workers	%	No. of workers	%	Total number	%
-20	36	2.8	24	2.3	24	6.5	84	3.1
20-29	185	14.2	136	12.9	83	22.4	404	14.8
30-39	405	31.2	381	36.2	112	30.3	898	33.0
40-49	389	29.9	282	26.8	84	22.7	755	27.7
50-59	210	16.2	185	17.6	37	10.0	432	15.9
60+	75	5.8	45	4.3	30	8.1	150	5.5
Total	1300	100.0	1053	100.0	370	100.0	2723	100.0

Table LVII shows the distribution of workers according to the duration of exposure to cotton dust. It can be seen that 19.2% were exposed for a period of less than 10 years while 80.8% were exposed for 10 years or more.

TABLE LVII Distribution of workers according to duration of exposure

Length of service years	Mill A No.	Mill A %	Mill B No.	Mill B %	Mill C No.	Mill C %	Total No.	Total %
-5	22	1.7	21	2.0	18	4.9	61	2.2
5-9	251	19.3	150	14.2	61	16.5	462	17.0
10-14	340	26.2	302	28.7	100	27.0	742	27.2
15-19	428	32.9	367	34.9	113	30.5	908	33.3
-20+	259	19.9	213	20.2	78	21.1	550	20.2
Total	1300	100.0	1053	100.0	370	100.0	2723	100.0

Prevalence rates of various diseases were calculated in the three mills.

Table LVIII shows that 7.7% of the workers developed simple bronchitis, 14.4% had chronic bronchitis, 4.7% were asthmatics while only 2.4% of the workers had emphysema. The prevalence of chronic bronchitis was higher (21.1%) among workers in mill C than among those in the other two mills (13.0% and 13.8% respectively). Also the prevalence of CNSPD was higher in mill C (39.1%) compared with the other two mills (26.9%). No cases of byssinosis were detected at any of the mills.

Table LVIII Distribution of cases in the different mills

Mills and (No. of workers)	A (1300)		B (1053)		C (370)		Total (2723)	
Disease	No.	%	No.	%	No.	%	No.	%
Simple bronchitis	91	7.0	82	7.8	36	9.7	209	7.7
Chronic bronchitis	169	13.0	146	13.9	78	21.1	393	14.4
Asthma	56	4.3	48	4.6	22	5.9	126	4.6
Emphysema	32	2.5	26	2.5	8	2.2	66	2.4
Total	348	26.8	302	28.7	144	38.9	794	29.2

Among the important factors contributing to the development of CNSPD is smoking. Table LIX shows the influence of smoking on the prevalence of CNSPD among workers of both sexes. It is apparent that the prevalence of CNSPD among male smokers is much higher than among female workers (44.7% versus 15.8%), the prevalence among non-smokers of both sexes is nearly the same (11.5% versus 11.6%) and the prevalence among smokers of either sex is higher than among non-smokers of the same sex.

Female smokers had a significantly higher prevalence of CNSPD than both male and female non-smokers but had a significantly lower prevalence compared to male smokers. This last observation can be explained by the fact that female smokers usually started smoking at an older age and smoked less, so, they had lower pack/year figures than males (8 compared to 21). Another cause is that male workers smoke "honey dew tobacco" (a mixture of tobacco and molasses), which is more irritating to the respiratory tract than cigarettes; none of the females had this habit while 38% of males did, in addition to smoking cigarettes.

Table LIX The influence of smoking on the prevalence of obstructive lung disease among male and female workers

	Males(1885)			Females (838)		
	No. of workers	No. of cases of CNSPD	Prevalence of CNSPD %	No. of workers	No. of cases of CNSPD	Prevalence of CNSPD %
Smokers	1623 (86.1%)	726 (96%)	44.7%	114 (13.6%)	18 (17.6%)	15.8%
Non-smokers	262 (13.9%)	30 (4%)	11.5%	724 (86.4%)	84 (82.4%)	11.6%
Total	1885 (100.0%)	756 (100.0%)	40.1%	838 (100.0%)	102 (100.0%)	12.2%

Table LX shows the dust concentrations in the work environment in the different departments of the three mills, the prevalence of CNSPD and the spirographic values of workers.

Table LX Dust concentration in the work environment in relationship to the prevalence of COLD and spirographic studies

Mill	Dept.	Number of workers	Cases	Dust conc. mgm/m^3	Prevalence of COLD	Ventilatory capacity %	FEV$_1$ %
A	1	253	92	0.52	7.1	91	73
A	2	465	130	0.72	10.0	82	71
A	3	582	126	0.89	9.7	84	69
B	1	138	52	0.45	4.9	92	75
B	2	396	112	0.69	10.6	81	73
B	3	519	138	1.05	13.1	80	72
C	1	370	144	1.25	38.9	78	64

COLD = Chronic obstructive lung disease.

The ventilatory function studies (VC and FEV$_1$%) of workers in the different departments of the three mills show a direct relationship with the environmental pollution. Thus low spirographic values are generally observed in places where the pollution is higher.

Question 5

The prevalence of CNSPD in the various departments did not correlate with dust concentrations as did ventilatory functions. What is the possible explanation?

PART 4

Conclusions

Results of the study revealed a high prevalence of CNSPD, but no cases of byssinosis. In an attempt to explain this and compare results obtained in this study with those from other regions in Egypt, results of studies reported in the world literature have to be consulted.

At a meeting of a WHO study group (WHO, 1983)) various reasons were given why the prevalence of byssinosis varied from one plant to another:

- The prevalence was found to be much higher in mills spinning coarse yarn from relatively low grades of cotton than in mills spinning either better grades or blends of cotton with synthetic fibres;
- In spinning rooms, prevalence figures varied in relation to plant design;
- In weaving, the prevalence varied from almost 0% to 13%;

- Differences in the treatment of yarn, in the amount of trash present at successive stages of processing and in some cases humidification and ventilation systems may account for such variations;

- The prevalence of byssinosis may be low in spite of high dust concentrations, if dust does not provoke a physiological response in the exposed workers. Examples of this kind of situation have been reported from a factory producing bleached medical cotton in Egypt, from a British mill processing cotton waste material, and from a Chinese study where cotton was washed prior to the manufacture of blankets (WHO, 1983);

- Subjects with characteristic symptoms of byssinosis may eventually develop an illness indistinguishable from CNSPD, but which is characteristically worse at the beginning of the work-week; at this stage the patient often forgets his early symptoms and is diagnosed as suffering from CNSPD (WHO, 1983); and

- A few epidemiological studies have shown strong correlation between the concentration of Gram negative airborne bacteria and the prevalence of byssinosis among workers in cotton spinning mills (Cinkotai & Whitaker, 1978).

Raylander, et al. (1979) in a study on 6708 card room workers from 23 textile mills in the USA found the prevalence of classical symptoms of byssinosis to be less than 1%. They found significant correlation, however, between dust concentrations and FEV_1 and between the latter and the counts of Gram negative bacteria in bale cotton.

Jones, et al. (1979) found the prevalence of byssinosis to be 5.7% in 386 cotton workers and that the disease was unequally distributed with respect to job category and mill rather than dust exposure levels. In an attempt to explain this, the authors suggested that it was due to variation in the biological potency of different samples of cotton dust, which they called "the mill effect". Factors which they thought may cause this effect are:

- the grade of cotton; and

- the industrial process - spinning produces a less dangerous dust than carding (milligram for milligram).

Other factors included:

- host (worker) resistance, subjects with hyperreactive airways may tend to leave dusty jobs earlier, leaving the more resistant ones; race, sex, atopy and innate factors; and

- variable response to questionnaires; enhanced awareness of respiratory symptoms and other sources of bias.

Question 6

In the present situation, what do you think is the reason for the observed regional differences in the prevalence of byssinosis?

Question 7

Does this study give a conclusive answer to Question 6?

Question 8

If the answer to Question 7 is no, what further suggestions do you have?

Question 9

Do you think CNSPD in textile workers should be made compensatable?

INSTRUCTOR'S NOTES
CHRONIC RESPIRATORY DISEASES IN COTTON TEXTILE WORKERS

This case begins with an observation of differential rates of compensation for byssinosis in two regions of Egypt. It illustrates the value of surveillance of occupational disease, then illustrates the use of a cross-sectional study to investigate prevalence rates of a group of respiratory diseases including byssinosis and chronic nonspecific pulmonary diseases.

The progression of the study includes the following steps:

1. Recognition of a problem, the discrepancy between surveillance data and study results from various plants and various regions of Egypt;
2. Review of the available information;
3. Design of the study, choice of the plants and testing of workers;
4. Analysis of results; and
5. Conclusions.

Answer 1

This question provides the opportunity to discuss the role of surveillance in the prevention of occupational disease. For purposes of discussion, surveillance can be defined as the collection, analysis, and use of health data for the purposes of prevention. The primary purpose of a workers compensation plan is to reimburse workers for the expenses of medical care, lost wages, etc. In this instance one role of the monthly meetings was to review or analyse aggregate data including trends of disease, variation in rates of compensation by region of the country, etc. One could imagine using data from workers compensation insurance programmes to identify particular plants that are contributing a disproportionate number of cases. Clearly by assessing the data from a workers compensation system, opportunities for prevention may be identified.

Answer 2

It is difficult to decide at this stage whether the differences in the prevalence of chronic respiratory diseases among textile workers are real or not. However, possible causes for the observed results are:

a) Lack of standardization of the criteria for diagnosis which might have lead to discrepancies between results of various studies; and

b) Underreporting to workmen's compensation may be due to (a) physicians having too high a threshold in making an appropriate diagnosis; (b) cases being misdiagnosed, which is unlikely due to the marked awareness about respiratory disease among those who work with cotton and their physicians.

A good deal of the information available in Egypt concerning cotton-related respiratory disease was reported not by the workmen's compensation, but rather by research institutions, which are fairly uniform regarding research techniques, diagnostic criteria and diagnostic tools (Noweir, *et al.* 1980; Noweir, 1981). Moreover, workmen compensation records have demonstrated that in other diseases such as lead poisoning, silicosis, industrial deafness, etc., results are fairly uniform throughout the whole country.

Answer 3

a) Talk with other research workers, industrial physicians, the occupational health and statistics departments at the health insurance and workmen's compensation systems and review the various steps for reporting occupational diseases in general and respiratory diseases in particular.

b) Critically review available information including prevalence rates of different chronic respiratory diseases, environmental data, duration of exposure in each study, diagnostic criteria and diagnostic tools, sensitivity and specificity of the tests used.

c) Review the literature from other countries for similar situations and their explanations.

d) Determine the need for further investigation in Egypt in an attempt to explain discrepancies in the prevalence of various respiratory disease.

Part 2

Answer 4

a) Collect preliminary information about the cotton textile industry in Egypt, its size, geographical distribution of plants, their number, working population, population at risk, medical services, details of different industrial processes, raw materials, quality of cotton, whether cotton is mixed with other fibres, environmental conditions and control measures.

b) Select a sample of cotton textile plants in Greater Cairo and Guiza region which represent fairly well the whole industry regarding diversity of industrial processes and which use essentially cotton. Older plants are preferable where the working environment is known to be dusty.

c) Visit the plants selected, study the industrial processes and make an evaluation of the working environment.

d) Review the industrial medical records.

e) Carry out a cross-sectional study to determine the prevalence of chronic respiratory diseases in the plants selected. Consider whether your goal is to confirm the presence of byssinosis in the one region or the absence of byssinosis in the other.

f) Two points have to be taken into consideration:
   i) The social security act requires that workers exposed to cotton dust be examined once every two years. Periodic medical examination is the responsibility of the health insurance system and it may be useful to coordinate with them. Perhaps the periodic medical examination in several plants could be augmented or modified so that they would be useful for research purposes.

   ii) Considering that the diagnosis of byssinosis is not easy and is based largely on subjective evidence, training of the survey team and standardization of the criteria for diagnosis of byssinosis (Qasim, 1977), bronchial asthma, emphysema and chronic bronchitis is of special importance. Therefore, careful selection of the survey team has to be ensured, highly qualified supervisors designated and adequate training carried out.

g) A meeting should be arranged between the senior research personnel, key persons at the health insurance system, industrial management and industrial physicians where the following will be discussed:
   i) Objectives of the study;

   ii) Methodology; and

   iii) The need for coordination and cooperation among the concerned parties and the need to review plant industrial hygiene records, and medical files as well as the workmen's compensation and health insurance records.

h) Industrial hygiene data were collected and measurements of dust concentrations made using personal samplers equipped with 10 mm nylon cyclones. Respirable dust concentrations were reported in various departments;

i) A sample of workers was selected by stratified random sampling from the various departments in the selected textile mills; the dustier operations were sampled preferentially including mixing, carding and spinning;

j) Health examinations were conducted. The main survey methods used were the following:
   i) Questionnaire on respiratory symptoms similar to that recommended by WHO (1983);

   ii) Clinical examination is of special importance since diagnosis of CNSPD is intended;

   iii) Ventilatory studies: the forced vital capacity and the FEV_1 were measured at the same time as the physical examination. Measurements before and after the shift need not be carried out since the essential element in diagnosis of byssinosis is the typical symptoms. The after-shift reduction of FEV_1 is not a prerequisite for the diagnosis nor is it specific for byssinosis; it is, however, a reliable index of work related airway obstruction (Qasim, 1977). Anthropometric data were taken and observed values compared with standard normal values of Egyptians.

iv) Smoking histories were taken and expressed in pack years.

v) Chest X-ray examination were carried out only to exclude other pulmonary and cardiac diseases.

PART 3

Answer 5

Contrary to byssinosis, CNSPD is a multifactorial disease. Previous studies have proved that although occupational dust exposures may have a definite influence upon the prevalence of CNSPD, the effect of smoking is usually more marked, therefore, masking any direct correlation between dust concentration and prevalence of CNSPD.

The observed impairment of ventilatory function might have represented a combination of the chronic effect, which would go hand in hand with the severity of CVNSPD, and the acute effect which would bear a relationship to the dust exposures at the time of measurement or immediately before. In the present study, the acute effect probably has predominated. No relation could be elicited between ventilatory functions on one the hand and the dust concentration and average duration of exposure on the other.

PART 4

Answer 6

a) In the plants studied as well as in textile plants studied in other regions, where byssinosis was diagnosed, the same quality of cotton was used, locally grown cotton which is hand picked and of a long-fibre. Plant debris content is not likely to be different.

b) The same industrial processes are being used.

c) Dust concentrations are rather high, sufficient to have caused byssinosis.

d) However, factors relating to temperature, humidity and storage of cotton may be different which would affect the growth and abundance of micro-organisms in the work environment. Host factors may also play a role.

Answer 7

The present study addresses the question of regional differences. Students may wish to discuss if this investigation resolves whether the cause for variation remains obscure, is due to differences in study techniques, diagnostic criteria or defects in the reporting system.

Answer 8

A future plan of research to study this question is to carry out a study in two groups of textile plants:

- One in which byssinosis was actually diagnosed, and another in which only CNSPD was found.

The study will compare:

- Raw material for type and grade of cotton chemical content such as protein, carbohydrate and minerals.
- Bacteriological examination of bale cotton at different times of storage.
- Industrial processes and control measures.
- Environmental conditions.

Medical studies will include:
- A questionnaire,
- Clinical examination,
- Ventilatory studies,
- Smoking histories,

And as deemed necessary:
- Biomedical,
- Microbiological and,
- Immunological studies.

Statistical analysis will focus on the relationship of various disease entities on the one hand to work processes and the chemical and microbiological characteristics of the work environment as well as the various "host" factors on the other.

Answer 9

CNSPD in the textile industry is certainly work related. The prevalence of the disease in the present study as well as in previous studies was high. The disease, however, is multifactorial and it is difficult to determine how much it is affected by nonoccupational causes in any individual case. This, nevertheless, should not be an obstacle to a serious reconsideration of the compensability of such cases.

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FARMER'S LUNG*

PART 1

Cases of farmer's lung have been reported in Australia, Canada, Europe and the USA. In China, chronic bronchitis has been studied extensively, but the hazards among farmers after exposure to vegetable dust is poorly realized. In 1978, the authors visited Dafeng County. Jiangsu Province, China, and found that the chief crops cultivated there were rice, wheat, corn, as well as cotton. The hay of these vegetable was ground into powder and utilized as pig feed. The rainfall in the area is abundant and the weather is rather humid. To the authors, the hay looked mouldy; during grinding, the air in the workplace was dusty. The authors predicted that workers were probably suffering from farmer's lung, although no such diagnosis had been made by local physicians.

Question 1

What is farmer's lung?

Question 2

Would you have looked for farmer's lung in that district?

Question 3

Why had not the disease been diagnosed there?

Question 4

How would you approach this problem?

PART 2

A preliminary study was conducted from 25 October 1978 until 10 November 1978 including a questionnaire and a medical investigation.

The process of hay grinding was simple and consisted of throwing hay into the inlet of a grinding machine and collecting hay powder in bags at the outlet. No dust control measures were taken. The air dust concentrations seemed high by visual inspection. No respirators or masks, nor any personal protective measures were used.

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* By Gu Xue-qi, Lu Pei-lian, Shen Yi-E, 1985. Revised 1986

A total of 105 grinders were investigated in five communes, among them, 12 grinders (11%) complained of systemic and respiratory discomfort, one to eight hours following grinding mouldy hay. The symptoms consisted of cough, expectoration, chest tightness, chills and fever. These symptoms subsided one to two days later, but would recur when exposure was repeated. Typical cases follow: Mr. Wu, a 27 year old male pig raiser complained on 22 October 1978, three hours after grinding mouldy hay, of dizziness, general malaise, anorexia, chills, soreness of the legs, shortness of breath, and chest tightness. Tetramycin and antipyretics were ordered. The symptoms subsided on the next day. Mr. Liu, aged 59, a male pig raiser complained on 23 October 1978, four hours after grinding mouldy hay, of chills, fever, general malaise, cough with phlegm, chest tightness and dyspnoea. He persisted on grinding for five days. The symptoms recurred in the evening and subsided spontaneously when he stopped grinding. On the same communes, 14 of 36 grinders of corn of good quality experienced mild cough and expectoration.

Question 5

What disease did the 12 hay grinders suffer from? Was it farmer's lung?

Question 6

What is your impression from this investigation to this point?

Question 7

How would you now proceed?

PART 3

The investigators conducted a questionnaire survey of 1054 hay grinders, including the pig raisers who ground hay, from nine communes and two farms in Dafeng County in 1980. It was found that 87 grinders complained of the same symptoms as described above. In a prospective component, in 1981-1982, the authors found another 33 grinders with similar complaints, totally 120 people. At the same time, an industrial hygiene survey of the processing environment was conducted. For purposes of comparison, another 107 healthy peasants with no history of grinding mouldy hay age and sex matched to the symptomatic cases were selected as controls.

Each of the grinders and of the controls were questioned about discomfort before the shift, and the body temperature and a physical examination of the respiratory system were made and the ventilatory function was tested at the same time. After four hour's grinding, all of the cases and referants were admitted to the local hospital for a medical examination. Subjective feelings, body temperature and chest physical examinations were recorded. White blood and differential counts and serum precipitin tests were conducted. Chest radiographs were taken ten hours after exposure.

The dust concentrations in air, dust dispersity and free silica content in the dust were analysed. Actinomycetes in the mouldy hay was looked after.

Question 8

What are the main points in diagnosis of farmer's lung?

Question 9

What findings would support the contention that farmers lung is prevalent in this providence?

Question 10

What is thought to be the etiology of farmer's lung?

Question 11

Is free silica responsible for farmer's lung? Why was it measured?

PART 4

The results of the survey follow:

1. Environmental monitoring: The average dust concentration in the breathing zone near the inlet of grinding machine was about 38.1 ± 24.9 mg/m^3, while near the outlet, it was 555.0 ± 60.1 mg/m^3. Of the dust particles 76.3% has diameter less than 5 micrometers. The free silica in the dust and in the hay samples is above 10% (25.5% - 38.3%). From 37 samples of mouldy hay and 31 samples of sputum, 80 strains of actinomycetes were isolated, 49 of them belong to *Thermoactinomyces vulgaris* (61.2%). No strain of *Micropolyspora faeni* was isolated.

2. Physical examination: Among the total of 120 exposed, 67 grinders exhibited symptoms of farmer's lung, including chills, fever, cough and shortness of breath. Most of the symptoms (97%) appeared four to eight hours after exposure. Positive physical signs were identified in 21 grinders, eight of them showing fine rales. Chest radiographs were taken in 101 grinders, showing a ground glass appearance in 21, small patchy infiltrates in 18, miliary opacities in nine, or distortion of lung markings in six (Table LXI), of which 14 were followed up. It was discovered that the patchy infiltrates and miliary opacities gradually cleared over seven days and totally disappeared four weeks later. But the reticular shadows and ground glass appearance persisted a year later. Pulmonary function testing showed a decline of ventilatory function. Of 119 grinders 55 showed an elevation of total white blood cell count. Although the eosinophil counts were increased in 67 grinders, no significant difference was seen between the exposed and the controls (Table LXII). Serum precipitins against antigens of *T. vulgaris* were found in 14 grinders, a significantly higher prevalence than in controls (Pepys, *et al*. 1963). Only one case had a positive response to the antigen of *M. faeni* (Table LXIII).

Table LXI Symptoms, signs and chest X-ray changes of the grinders

Symptoms (120-grinders)	Number	Signs (120-grinders)	Number	Chest X-ray changes (101-grinders)	Number
Cough	95	Fever (>37.5°C)	17	Ground glass appearance	21
Chills	71	Fine moist rales	8	Small patches	18
Fever	61	Dry rales	4	Miliary opacities	9
Dizziness	60	Wheezing	4	Reticular shadows	6
Shortness of breath	30	Crepitation	1	Distortion of lung marking	6
Chest tightness	23	Barrel chest	5	Emphysema	5
Expectoration	12	Positive respiratory signs	21		
Headache	10				
Wheezing	7				
Chest pain	3				

Table LXII Comparison of laboratory parameters between exposed and controls

	Total WBC counted		Percentage of neutrophiles		Absolute count of eosinophils	
	Exposed	Control	Exposed	Control	Exposed	Control
Number of persons counted	119	30	119	30	119	30
Number of persons with elevated result	55	1	76	5	67	14

Table LXIII Response to antigens of farmer's lung expressed by serum precipitins

Groups	Number of persons	Antigens of M. faeni, number of positive	Antigens of T. vulgaris, number of positive
Exposed	30	1	14
Control	30	0	1

Question 12

Calculate the percentages for the tables in Part IV.

Question 13

What is your conclusion from this survey?

Question 14

What is the etiology of farmer's lung in this district?

Question 15

Suggest preventive measures.

PART 5

The preventive measures instituted include:

1. Health education:

a) Training of primary care personnels at the farm and commune levels in order to provide medical care for the hay grinders; and

b) Spread propaganda among the masses about the knowledge of farmer's lung and its controls, especially among the hay grinders in order to encourage their acceptance of the control measures.

2. Preventive measures:

a) If possible, the use of refined feed instead of mouldy hay as pig feed.

b) Keeping the hay dry before being piled up to prevent the growth of mould, and then keeping the stack out of the rain.

c) Dust suppression is needed during grinding, such as collecting the powder at the outlet in an enclosed bag or isolating the outlet from the other operations.

d) Provision of respirators to the grinders.

e) Periodic medical examination and environmental monitoring must be conducted for grinders and their workplaces by the health department.

Question 16

How will you evaluate the effectiveness of these procedures?

Question 17

Do you expect these preventive measures to be effective?

INSTRUCTOR'S NOTES
FARMER'S LUNG

These cases progressed from the observation that a well-known disease may exist in an area, where locally it is not recognized, through the conduct of a questionnaire, a medical, and an industrial hygiene survey to confirm the presence of the disease, and ended with a probing question of how one should evaluate the effectiveness of recommendations in preventing disease. This case is most appropriate for the student novice ,who needs an introduction to basic epidemiology as well as to the evaluation of public health interventions.

PART 1

Answer 1

What is farmer's lung?

Farmer's lung is one kind of extrinsic allergic alveolitis (Terho, 1982), caused by inhalation of mouldy hay or other mouldy vegetable dusts which contain spores of certain Thermoactinomyces. Its clinical features reflect the response to the extrinsic allergen in the peripheral zone of the bronchopulmonary tree where it causes impairment of gas exchange.

Answer 2

Do you think that farmer's lung may exist in that district?

Yes, the environmental conditions were favorable to mould growth in hay. Actually mouldy hay was seen in the district when the authors visited there. The air in the workplace was heavily polluted by hay dusts during grinding.

Answer 3

Why had not the disease been diagnosed there?

Workers, especially local doctors were not aware of the entity of "farmer's lung" before the visit of the authors. The symptoms of an acute episode of farmer's lung is very similar to an upper respiratory infection, i.e., chills, fever, cough and breathlessness. These symptoms would subside spontaneously in a short period after separation from grinding. Therefore, it was mistakenly diagnosed as "common cold". Moreover, since the course of the disease is rather short, the patient is usually does not see a physician. Also contributing to the physicians' failure to associate these symptoms with exposure to mouldy hay, is the low incidence of the clinical entity.

Answer 4

How would you plan a preliminary investigation in that district?

A preliminary approach might be to conduct a questionnaire survey in order to determine if workers had experienced the syndrome of typical complaints and if there were an association with exposure to hay grinding.

PART 2

Answer 5

What kind of disease did the 12 hay grinders suffer from? Was it farmer's lung?

They seemed to suffer from farmer's lung. The reasons would be as follows:

a) The symptoms appeared recurrently after exposure to mouldy hay dust and subsided spontaneously after removed from exposure. This indicated that the symptoms were related to exposure to mouldy hay dust.

b) There was a latent period of one to eight hours from exposure to onset of symptoms. This time interval together with symptoms is consistent with an acute episode of farmer's lung.

Answer 6

What is your impression so far from this investigation?

By virtue of the preliminary investigation, it could be said that there existed environmental factors for farmer's lung, and that some grinders had a history consistent with this disease. But a clear-cut conclusion could not be given, since no objective evidence has yet been obtained.

Answer 7

How can you further confirm the result already gained?

A follow up clinical observation of response of grinders after exposure to mouldy hay dust could be conducted, and clinical surveillance and hygienic monitoring of the working environment should simultaneously be conducted in order to obtain objective evidence for further confirmation of the result already gained.

PART 3

Answer 8

What are the diagnostic criteria for farmer's lung? They are as follows (Crofton & Douglas, 1981):

a) Occupational history of exposure to mouldy vegetable (hay) dust;

b) Latent period of four to eight hours between exposure and acute onset of farmer's lung symptoms;

c) Symptoms including chills, fever, cough and breathlessness;

d) Miliary shadows and small patches or no changes on chest X-ray films, if X-ray examination could be taken; and

e) Positive precipitin response to certain farmer's lung antigens in serological test in some victims, if laboratory facilities are available.

d) and e) may be used as options.

Answer 9

What results do you predict in this situation?

The results predicted may be:

a) The air concentration of mouldy hay dust in workplace;

b) Whether the clinical features among the grinders after exposure coincide with the main points mentioned above; and

c) Finding the causative agents of farmer's lung in that district.

Answer 10

What is the etiology of farmer's lung generally considered?

They are the Thermoactinomyces. The most commonly found is Micropolyspora faeni and the next, Thermoactinomyces vulgaris.

Answer 11

Is free silica responsible for farmer's lung? How can you evaluate it?

Free silica in the dust is not responsible for the acute episode of farmer's lung, since (1) silicosis caused by free silica is a chronic lung disease with no acute episode; (2) silica dust can induce a response of the respiratory mucosa, but no systemic reaction, such as chills, fever, etc; (3) the pathological change in silicosis is irreversible fibrosis, but those on the chest X-ray films of acute stage of farmer's lung may subside some weeks later.

PART 4

Answer 12

Calculate the percentage and X^2 analysis in the following tables.

372

Table LXI Symptoms, signs and chest X-ray films' changes of the grinders

Symptoms (120 grinders)	No.	%	Signs (120 grinders)	No.	%	Chest X-ray films' changes (101 grinders)	No.	%
Cough	95	79.2	Fever (>37.5°C)	67	55.8	Ground glass appearance	21	20.8
Chills	71	59.2	Fine moist rales	8	6.7	Small patches	18	17.8
Fever	61	50.8	Dry rales	4	3.3	Miliary opacities	9	8.9
Dizziness	60	50.0	Wheezing	4	3.3	Reticular shadows	6	5.9
Breathlessness	30	25.0	Crepitation	1	0.8	Distortion of lung markings	6	5.9
Chest tightness	23	19.2	Barrel chest	5	4.2	Emphysema	5	5.0
Expectoration	12	10.0	Positive respiratory signs	21	17.5			
Headache	10	8.3						
Wheezing	7	5.8						
Chest pain	3	2.5						

Table LXII Comparison of laboratory parameters between exposed and controls

	Total WBC counted		Percentage of neutrophiles		Absolute count of eosinophils	
	Exposed	Controls	Exposed	Controls	Exposed	Controls
Number of persons counted	119	30	119	30	119	30
Number of persons with elevated result	55	1	76	5	67	14
%	46.2	3.3	63.9	16.7	56.3	46.7
X^2	18.80	21.51	0.90			
p	0.001	0.001	0.05			

Table LVIII Response to antigens of farmer's lung expressed by serum precipitins

Groups	Number of persons	Antigens from *M. faeni* Number of positive responses	%	Antigens from *T. vulgaris* Number of positive responses	%	X^2	p
Exposed	30	1	3.3	14	46.7	12.8*	0.001
Controls	30	0	0	1	3.3		0.05**

* Yates' correction

** Fisher's exact test

Answer 13

What is your conclusion from this survey?

The conclusion is as follows: (1) The workplace dust concentration in air is rather high. According to Chinese maximal acceptable concentration (MAC) standard of dust, this concentration exceeds the MAC 18-276 times. The Chinese MAC for dust with free silica above 10% is limited to $2mg/m^3$. It is also 4.22-17.43 times above the TLV ($15mg/m^3$) of nuisance dust recommended by OSHA of the USA. (2) Acute responses were observed among those farmer's lung victims when they had exposure to high concentrations of mouldy hay dust. These responses were in keeping with the diagnostic criteria of farmer's lung. (3) The free silica content in the mouldy hay dust is relatively high. It was well known that long-term exposure to it would induce interstitial fibrosis of lungs. In this survey, the acute response was unlikely to be related to free silica, but the possible role of free silica in interstitial fibrotic changes of lung should not be neglected.

Answer 14

What is the main etiology of farmer's lung in the district?

According to the result of serum precipitin test and the isolation and identification of *Thermoactinomyces* in mouldy hay, it was shown that the main etiological agent of farmer's lung in that district was *T. vulgaris*. But, since the dust concentration in air was very high, the role of pathogenic action of dust itself was opened to further investigation.

Answer 15

Suggest preventive measures.

The preventive countermeasures include: (1) Aiming at etiology: preventing mouldy change of hay in order to eliminate the factors favoring to proliferation of *Thermoactinomyces*, (2) Aiming at external factors influencing the pathogenesis: preventing generation of dusts, (3) Protecting susceptible persons: accepting effective protective measures, (4) Medical supervision and environmental monitoring.

PART 5

Answer 16

How would you evaluate the effectiveness of the control measures?

Assessment of the effectiveness of preventive measures may depend on: (1) environmental monitoring: a) determination of air dust concentration, b) determination of the concentration of *Thermoactinomyces* spores in air if possible, c) detection of the degree of mouldy change of hay, (2) medical surveillance to find out the incidence of farmer's lung among the exposed group.

Answer 17

What do you expect about the effectiveness of these preventive measures?

If these measures can be put into practice, the incidence of farmer's lung should decline significantly. But actually there are a number of obstacles, such as, the mouldy change in the hay is closely related to the rainfall after harvest; the dust control measures are sometimes limited due to economic resources; the respirators worn by the grinders must be highly effective to filtrate out the spores of Thermoactinomyces with diameters of 1 micrometer. The gauze masks generally used are not adequate for this purpose. Besides, the grinders would not like to wear respirators during heavy labor, due to the difficulty of breathing and the discomfort of the respirator.

Through medical education the grinders in Dafeng County have realized that mouldy hay dust is harmful, and that the disease could be controlled through preventive measures. They always treat and pile it up carefully to avoid mouldy changes. At the same time, since the financial condition of the peasants has improved greatly, and rice production has increased markedly, the peasants have begun to use cotton seed cake, wheat or wheat bran to raise the pigs instead of hay. All these are the fundamental measures that have contributed to the reduction of farmer's lung in Dafeng County. Fourty five grinders with a history of farmer's lung were visited in October, 1985. 60% (27) of them have not ground hay since 1982. Only nine among the 45 grinders had an acute episode of farmer's lung during 1983-1985. So approximately 80% of the grinders were effectively protected. In two communes, the incidence of acute episodes of farmer's lung was reduced among 170 grinders in 1980, 1983, 1984, and 1985 from 27%, 10%, 7%, and 2% respectively.

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EPIDEMIOLOGY IN THE DEVELOPMENT OF OCCUPATIONAL HEALTH SERVICES*

Part 1

Background

Many developing countries are undergoing rapid industrialization involving changes in methods of work, new industrial processes and new occupational health and safety hazards. Quite often, this industrial development has not been associated with a corresponding development of an occupational health programme.

Your country is a developing one, and you are a qualified occupational health specialist. The information available on workers' health is very scarce and the national occupational health services are very weak. Laboratory and portable equipment are lacking, trained personnel are in short supply, priorities need to be identified, occupational health hazards are said to exist but their types and magnitude are not known. You felt the necessity for developing an adequate occupational health programme. You decided to carry out a field investigation to find out the types and magnitude of health problems affecting the working populations; first, to serve as a guide to the need for introducing control measures of outstanding problems; second, to identify priorities in programme development including legislation, health manpower needs, and research; and third, to serve as a base-line for the evaluation of health trends with the changing work-environment and methods, and to be used as a measure of the effectiveness of any preventive measures introduced.

You selected an industrial area or district which has more than 1500 industries; many are small (up to 50 workers), or medium-sized (51-150 workers) and some are large (more than 150 workers). The Ministry of Health provided you with a team of physicians, sanitarians and nurses for this survey. You realized that it was not practical to survey all the factories and examine thousands of workers. Most of the large factories had medical units which maintained some records. You decided to give priority in this first survey to the small- and medium-sized plants.

Question 1

Why do you give priority to small- and medium-sized factories for your investigation?

Question 2

Outline the possible objectives of this investigation, bearing in mind the identification of needs in workers' health and the possible differences in health status of the workers relating to the type and size of workplaces.

Question 3

What should you do first with the survey team, and what information would you require them to collate on the work environment and workers' health in order to obtain meaningful data for the stated objectives?

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* By Batawi, M.A., and Husbumrer, C. (1985)

PART 2

You discover from the official records that there are 972 small- and medium-sized plants in the area, employing a total of 5 454 workers. Given the limitations of personnel in your team and the shortage of time to provide the Ministry of Health with information that would help in decision making, you decided to examine a representative sample of these work places and of the workers employed in the selected workplaces.

Question 4

How would you proceed with selecting a sample of workplaces stratified by type and size?

Question 5

In the workplaces selected, how would you proceed with sample selection of the workers, bearing in mind, that certain groups of workers may be particularly exposed to specific occupational health hazards?

Option 1

Make a "systematic" sampling of all the workers regardless of exposure.

Option 2

Make a "systematic" sampling of all non-exposed or partially exposed workers to various hazards and in addition, examine all the workers that are clearly exposed to specific hazards.

a) Which of these two options would you choose, bearing in mind your objectives?
b) How do you draw a "systematic" sample comprising 20% of workers in each selected plant?
c) Are there other methods of sample selection?

Question 6

What are the possible biases that you should bear in mind in selecting "representative" samples of workplaces and of workers for undertaking health surveys?

PART 3

From a total number of 972 small and medium-sized industries, approximately 10 % were selected for this survey. The sample was stratified by the type of industry and by the size of workplaces; small (up to 50) or medium (51-150). Plants over 150 workers were excluded in this investigation. Table I shows the total number of the small- and medium-sized industries from which the sample was drawn and the total number of workers employed in these factories. The number of the workplaces selected and the workers examined are also shown. Table II shows the distribution of the plants surveyed by type and size, and Table III shows the sex distribution of the workers examined in various types of industries.

TABLE I

Size of plant (No. of workers)	Plants		Workers	
	Total No. in area	No.surveyed (%)	Total employed	No. examined (%)
Small (up to 50 workers)	557	56 (10.1)	1 417	326 (23.0)
Medium (51-150 workers)	415	40 (9.6)	4 037	1 123 (27.8)
Total	972	96 (9.9)	5 454	1 449 (26.6)

TABLE II

Size of plant (No. of workers)	Type of Plant						
	Printing & batteries	Chemical	Textiles	Workshops	Ceramics & glass	Other	Total
Small (up to 50 workers)	6	9	10	18	6	7	56
Medium (51-150 workers)	4	14	7	5	4	6	40
Total	10	23	17	23	10	13	96

TABLE III

Industry	No. of factories surveyed	No. of workers employed	Workers examined			Sample size (%)
			Males	Females	Total	
Printing & battery	10	951	188	80	268	28.1
Chemical	23	1529	275	110	385	25.2
Textile	17	1219	150	153	303	24.8
Workshops	23	927	191	66	257	27.7
Ceramics & glass	10	424	101	20	121	28.5
Other	13	404	51	64	115	28.4
Total	96	5454	956	493	1449	26.6

Question 7
What observations do you have on Tables II and Table III?

PART 4

Table IV shows the distribution of the workers examined by age and sex in the plants surveyed. The same trend in the age distribution occurred in the six categories of workplaces.

TABLE IV

Age group (Years)	Male		Female		Total	
	No.	(%)	No.	(%)	No.	(%)
20 or under	345	(36.1%)	272	(55.2%)	617	(42.6%)
21 - 30	451	(47.1%)	156	(31.7%)	607	(41.9%)
31 - 40	106	(11.1%)	47	(9.5%)	153	(10.6%)
41 - 50	31	(3.2%)	15	(3.0%)	46	(3.1%)
51 - 60	19	(2.0%)	3	(0.6%)	22	(1.5%)
61 - 80	4	(0.4%)	-	-	4	(0.4%)
Total	956	(100%)	493	(100%)	1 449	(100%)

Question 8

From Table IV, it is clear that the age of the workers in these industries are mostly up to 30 years. What possible explanation do you give for this observation?

Question 9

In Table IV there are differences in age and sex distribution in the young groups (up to 30 years). What are these differences? Any possible explanation?

Question 10

Mention some of the possible occupational health implications of the age factor where mainly young workers are employed?

PART 5

An overall description of health and safety provisions in the plants surveyed according to their size is shown in Table V. There are clear and "consistant" differences between the small- and medium-sized industries in sanitary provisions, medical and nursing care, safety provisions, and the availability of environmental control measures.

TABLE V

Size of plant	Plants surveyed	Sanitation		Medical and/or nursing		Safety provisions		Control measures (e.g. Ventilation)	
		absent No. (%)	present No. (%)	absent No. (%)	present No. (%)	absent No. (%)	present No. (%)	absent No. (%)	present No. (%)
Small (up to 50 workers)	56	45 (80)	11 (20)	55 (98)	1 (1)	44 (77)	12 (21)	45 (80)	11 (20)
Medium (51 - 150 workrs	40	22 (55)	18 (45)	34 (85)	6 (15)	23 (57)	17 (43)	28 (70)	12 (30)
Differences in frequency, medium versus small.		25%		14%		22%		10%	

A further analysis of the conditions of work and the types of health hazards are shown in Table VI for the small and the medium-sized plants.

Table VII shows the distribution of the health hazards by type of industry.

In both, Table VI and VII, the following terms are used: (i) exposure to "dusts" which included both vegetable and mineral dusts, the former being encountered in the textile industries; (ii) although no measurements were made of environmental temperature, exposure to heat stress was recorded when the industrial process included smelting processes, or furnaces, or the workers showed manifestations of heat stress, e.g. sweating; (iii) exposure to noise was described as present when individuals in the survey team were obliged to raise their voices in order to communicate with each other; (iv) inadequate lighting included dim or dark areas in the workplace as well as obvious glare in such operations as welding in workshops and in the battery factories; (v) the term "accident potential" was meant to include such conditions as: absence of machine guards in hazardous operations e.g. circular saws; inadequate layout of machinery and raw material; unsafe construction of the plant which, in some instances, had some areas that were improperly constructed, but simply patched with bamboo or a wooden wall; and slippery floors, protruding objects in areas which are frequented by the workers; and (vi) "other toxic exposures" included a variety of risks, for example exposure to welding fumes, solvents, and potential exposure to metal fumes in the workshops.

TABLE VI

Size	No. of plants surveyed No. (%)	Lead fumes and vapours No. (%)	Irritants (gases, fumes smoke) No. (%)	Dust No. (%)	Heat stress No. (%)	Excessive noise No. (%)	Inadequate lighting No. (%)	Accident potential No. (%)	Other toxic exposures	Total No. of hazards	Average No. of hazards per plant
Less than 50	56	11 (19.6)	26 (46.4)	17 (30.4)	17 (30.4)	28 (50.0)	30 (53.6)	37 (66.1)	5 (8.9)	171	3.1
51 - 150	40	6 (15.0)	21 (52.5)	10 (25.0)	13 (32.5)	8 (20.2)	12 (30.0)	20 (50.0)	3 (7.5)	93	2.3
Total	96	17 (17.7)	47 (48.9)	27 (28.1)	30 (31.3)	36 (37.5)	42 (43.8)	57 (59.4)	8 (8.3)	264	2.8

Risk ratio = 1.34

TABLE VII

	No. of factories surveyed	Lead fumes and vapours	Irritants (gases, fumes, smoke)	Dusts	Heat stress	Excessive noise	Inadequate lighting	Accident potential	Other toxic exposures
Printing and batteries	10	7	6	-	2	4	3	4	-
Chemical	23	2	12	4	3	3	8	15	2
Textiles	17	-	9	10	5	15	6	7	1
Workshops	23	7	12	5	7	9	14	21	4
Ceramics and glass	10	1	4	5	8	2	5	4	1
Others	13	-	4	3	5	3	6	6	-
Total	96	17	47	27	30	36	42	57	8

Question 11

a) What observations do you note in Tables V, VI and VII?

b) Can you relate any of these observations to earlier data in Table II?

c) Do you find "consistency" in the results obtained in the differences that may be attributed to the size of the plants surveyed, e.g. in Table V;

d) What statistical tests to verify significance of observed differences would you carry out?

PART 6

The prevalence of various diseases in the small and medium-sized industries is shown in Table VIII. Consistently, a higher prevalence of the diseases, diagnosed by the investigators, was found in the small factories. Two main observations were noted; first with respect to lead poisoning or manifestations where 22 % of the workers in the small factories were affected as compared to 7% in the medium-size industries; and the second concerns gastrointestinal health problems, where more than one third of the workers examined in the small industries were affected compared to 10 % in the medium industries. Lead "poisoning" or absorption was recorded when the exposed workers

a) showed lead lines in the gums, and

b) gave symptoms such as colic, and constipation, a few of them showed signs of anemia and pallor.

TABLE VIII

Size of plant	Total No. of workers examined	Lead poisoning or absorption No. (%)	Dermatitis No. (%)	Upper resp. tract symptoms No. (%)	COPD* No. (%)	Gastro-intestinal No. (%)	Neuro-logical No. (%)	Mal-nutrition No. (%)	Others No. (%)	Workers with no illness diagnosed No. (%)	Total No. of illnesses No. (%)
Small (up to 50 workers)	326	73 (22.4)	9 (2.8)	89 (27.3)	20 (6.1)	115 (35.3)	19 (5.8)	8 (2.5)	10 (3.1)	129 (39.6)	343
Medium (51-150 workers)	1 123	79 (7.0)	27 (2.4)	208 (18.5)	56 (5.0)	117 (10.4)	24 (2.1)	21 (1.9)	24 (2.1)	616 (54.9)	556
Total	1 449	152 (10.5)	36 (2.5)	297 (20.5)	76 (5.2)	232 (16.0)	43 (3.0)	29 (2.0)	34 (2.3)	745 (51.4)	899

* COPD = Chronic obstructive pulmonary disease

The cases of dermatitis were all found in the workers handling mineral oils, acids and alkalis. While lead poisoning and dermatitis are mainly occupational in origin, the upper-respiratory tract symptoms and chronic obstructive pulmonary disease (COPD) may be related to pollution in the work environment and smoking habits.

Gastrointestinal (GI) health problems included cases of dyspepsia, indigestion, peptic ulcer, and irregularity of stools including intermittent diarrhoea. It was not possible to assess the degree of work-relatedness of gastrointestinal problems, particularly as they appeared in different prevalence rates in the various occupations, without any significantly higher occurrence in any particular occupation.It is likely, without totally excluding work-relatedness, that the GI diseases were endemic problems affecting the general population. However, they occur in a higher magnitude in the small factories, then in medium ones (35.3 % against 10.4 %), but this could be related to the fact that the small industries largely lacked sanitary provisions (see Table V) and that the workers employed there generally come from a poorer sector of the community.

Malnutrition appeared in 2 % of the total population and this mainly included cases of undernutrition.

The diseases classified under "Others" included various surgical and gynecological problems, for example hernias, lipomas, irregular menstruation, a variety of vague symptomatology and ten cases of pulmonary tuberculosis.

Question 12

In examining Table VIII you can develop a four-fold table demonstrating differences in disease occurence in small-scale industries as compared to medium ones (Table IX). Thus by deducting the number of workers with no illness diagnosed from the number of workers examined you obtain the number of worker with illness; thus

Table IX

Industry	Health problems Yes	 No	Total
Small	197	129	326
Medium	507	616	1123
Total	704	745	1449

Calculate X^2 for significance.

Question 13

On further examination of Table VIII, the total number of illnesses is greater than the number of workers with illness in both the small- and medium-sized industries, demonstrating that sick workers had an average of more than one disease. Construct a table to illustrate this observation and comment on differences between workers in small- and medium-sized industries. Are these differences meaningful?

PART 7

TABLE X

Industry	Workers examined	Lead manifestations No. (%)	Dermatitis No. (%)	Upper resp tract infections No. (%)	COPD No. (%)	Gastro-intestinal No. (%)	Neuro-logical No. (%)	Malnu-trition No. (%)	Others No. (%)	Workers diagnosed with no illness No. (%)
Printing & battery	268	101 (37.7)	2 (0.7)	16 (6.0)	1 (0.3)	30 (11.2)	7 (2.6)	7 (2.6)	1 (0.3)	119 (44.4)
Chemicals	385	2 (0.5)	14 (3.6)	70 (18.2)	12 (3.1)	47 (12.2)	15 (3.9)	4 (1.0)	17 (4.4)	220 (57.1)
Textiles	303	- -	- -	140 (46.2)	40 (13.2)	39 (12.9)	9 (3.0)	2 (0.7)	12 (3.9)	130 (42.9)
Workshops	257	30 (11.7)	16 (6.2)	40 (15.6)	4 (1.6)	58 (22.6)	12 (4.7)	9 (3.5)	1 (0.4)	140 (54.4)
Ceramics & glass	121	19 (15.7)	1 (0.8)	14 (11.6)	15 (12.4)	32 (26.4)	- -	4 (3.3)	2 (1.7)	72 (59.5)
Others	115	- -	3 (2.6)	17 (14.8)	4 (3.5)	26 (22.6)	- -	3 (2.6)	1 (0.9)	64 (55.6)
Total	1 449	152 (10.5)	36 (2.5)	297 (20.5)	76 (5.2)	232 (16.0)	43 (3.0)	29 (2.0)	34 (2.3)	745 (51.4)

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391

PART 7 (cont.)

Table X shows the prevalence of different diseases among the workers examined in each type of industry. Of the workers employed in printing and battery workshops, 37% showed manifestations of lead poisoning, as did 16% of the workers in ceramics and glass industries, probably due to absorption of lead used in glazing of ceramics and the addition of lead to glass in smelting processes. Occupational dermatitis was highest in the workshops where cutting-oils were frequently used. Upper-respiratory tract diseases and COPD occured in higher proportions among the textile workers, probably due to inhalation of vegetable dusts. Gastrointestinal, neurological, malnutrition and other health problems did not show significant differences in prevalence in any one single occupational group.

The designation of "free" signified an absence of abnormalities and symptoms in the clinical examination. When the "free", or normal cases are deducted in each type of industry from the total workers examined in each of these industries, it should be noted that there were a total of 899 cases of diseases affecting 804 workers, which means that there were a number of workers affected by more than one disease.

Question 14

Do you have observations to make on Table X?

Question 15

a) In spite of the shortage in equipment, do you find that this study produced useful information that can help in working on the problems of occupational health in your country? - If yes, in what manner?

b) What is the type of this epidemiological study, and what follow-up do you wish to see made?

INSTRUCTOR'S NOTES

EPIDEMIOLOGY IN THE DEVELOPMENT OF OCCUPATIONAL HEALTH

Summary

This case demonstrates the use of epidemiology in planning and implementation of occupational health services in a developing country. It provides an example of an investigation in an industrial district of a selected sample of workplaces stratified by type and size, together with a medical examination of a representative sample of the workers employed in the selected industries. The types of health problems affecting the workers, the health hazards in various industries and the differences between small-scale industries and medium-sized ones were identified. The study revealed the occurence of occupational and other work-related diseases affecting the workers particularly in the small-scale industries. This data helped the health authorities in developing an occupational health programme to deal with these problems. That programme included training of personnel, the development of a new cadre in primary health care in the workplaces, the proposal of new legislation and the establishment of specialized laboratories. Similar investigations were also planned for other areas. A follow-up study is underway to evaluate the effectiveness of the control measures introduced, as well as the results of commencing a primary health care system in the workplaces.

PART 1

Answer 1

Small- and medium-sized industries were given priority for this first investigation because of the following:

a) They comprise the majority of workplaces in many countries, and play a major role in national industrial production;

b) they often lack health provisions including medical, nursing, hygiene and safety services;

c) they are rarely reached by regulatory supervision and inspection because they are widespread and numerous, in spite of their potential health and safety hazards; and

d) they have lower economic and technological standards than larger factories and employ semi-skilled workers with limited experience in safety. These workers may work longer hours and receive lower wages than those in large industrial establishments.

Answer 2

The possible objectives of this investigation are:

a) To identify the types and magnitude of health problems of workers employed in small (up to 50 workers) and medium-sized industries (51-150 workers) in the industrial district with a view of introducing control measures of the health hazards identified; and

b) To obtain information on the health status of workers in these sectors to assist in developing national occupational health services, and to help in follow-up action by monitoring.

Answer 3

The survey team should first be trained briefly in occupational health and on survey methods. Information should be collated in a standardized manner, using a standard format including the particulars of the plant, a description of processes, potential health and safety hazards, particularly chemical and physical factors and other risks that might lead to injuries; control measures available, e.g. ventilation, machine guards, personal protective equipment; sanitary facilities; availability of health and safety personnel (on a full or part-time basis), accessibility to health care units, availability of pre-employment and periodic health examination and of health and safety records should be noted; and other elements, e.g. type of machinery and plant construction and layout recorded.

Medical examination of workers was carried out using also a standard format. The information obtained included age and sex, social and occupational histories, past medical history, complaints if any, personal habits (e.g. smoking). In case of exposure to specific chemical or physical factors, special enquiry was made about related signs and symptoms. Some workers required chest X-rays. In view of the fact that lead exposure was suspected to occured, such signs as lead line in the gums associated with abdominal colic and/or constipation were taken as indication for lead absorption or toxicity.

Although the survey team did not use any laboratory or portable equipment to make measurements of environmental hazards or to ascertain the diagnosis of occupational diseases, the main objectives of the study were achieved by detailed survey of workplaces and examination of work people.

PART 2

Answer 4

- First: determine a "representative" and feasible sample-size; i.e. the number and percentage to be surveyed;
- second: classify the 972 industries according to size which, arbitrarily, was decided; thus those employing up to 50 workers were considered "small", and those having 51 to 150 workers were considered "medium"-sized industries;

- third: classify each group according to type of manufacturing;
- fourth: from each of the two groups (by size) classified by type select systematically from lists of plants in serial numbers every 10th factory, number 10, 20, 30, etc. or number 2, 12, 22, etc. The factories selected constituted six different types of manufacturing:

a) printing and battery (as one group because of the known potential exposure to lead in each); b) chemical plants including electroplating, small transformation process, preparation of certain acids and alkalis, formulations and packaging of pesticides, preparation of cleaning materials such as detergents and soap, etc; c) textiles constituting mainly cotton carding, spinning, or only weaving and dyeing; d) workshops including a variety of industries such as blacksmiths or small foundries, carpentry operations, assembly of small products including one for bicycles, repair workshops for cars and trucks; e) the ceramic and glass workplaces: ceramics included clay preparation, shaping on wheels, firing, glazing and further firing. The glass factories used mainly old broken glass as raw material sorted by color then melted, and blown in moulds for bottles or glasses; and f) "other" workplaces: these included miscellanious types plants such as clothing- manufacture and food processing.

Answer 5

After deciding on the sample size (20%) of the workers to be examined in the selected plants

a) Option 2 was chosen in view of our interest in identifying occupational diseases in so far as possible (with limited means for diagnosis) in order to put them under control.

b) the workers selected for medical examination constituted around one-quarter of the workers employed. Selection was made systematically, i.e. every fifth name from payroll lists (20%). In addition, those workers that were particularly exposed to specific health hazards, e.g. lead fumes or respiratory irritants were all examined making a total of 26.6% (Table I, Part 3).

c) Other methods include using random numbers amounting to the sample size.

Answer 6

The possible bias is the fact that each factory is an entity of its own that may be totally different from other factories with respect to conditions of work, control measures taken, socioeconomic standards of the workers regardless of the plant size or its type of manufacturing. True representation of the whole may therefore be affected by unusually good or bad workplaces in the different clusters.

PART 3
Answer 7

Observations on Table II:

The fact that "workshops" represented the largest "type" in the small plants surveyed; 10 out of 56 or 32%. On the other hand "chemical" plants represented the largest type in the medium-sized factories; 14 out of 40 or 35%.

Observations on Table III:

The fact that the number of female workers as compared to males was less than half in four out of the six types classified. The two exceptions were in "textiles" and "others" where these were almost equal numbers, slightly more females.

PART 4
Answer 8

There were two possible explanations for the markedly small number of workers above the age of 30 years:

a) The relatively low wages of workers in small- and medium-sized industries leads to the workers' departure as they reach the age of 30 to advance their careers and provide for better family support. The other jobs to which they usually move include trade and commerce, and service industries, as well as similar occupations in larger and better paying industries.

b) Employment in small- and medium-sized industries is usually associated with more health hazards than in larger and more modern industries, which enjoy better environmental conditions, health and welfare facilities. As young workers gain experience in the small- and medium-size factories, they move to larger industries doing similar but healthier and safer work.

Answer 9

Table IV shows the distribution of the workers examined by age and sex; 42.6% were under the age of 20 years. The females in this age group represent a majority of 55.2% of all the females in the sample. The age group 21 to 30, constituted almost 42% of the total. In this age category the males represent the majority (47.1% males against 31.7% females). After the age of 20 years the females may leave (8.9%) to get married.

Answer 10

a) Possibly a higher accident rate in younger age groups;
b) there would not be enough time of exposure to develop or observe chronic diseases or occupational diseases with long latent period despite the exposures described e.g. silicosis or cancer.

PART 5

Answer 11a)

Observations on Table V:

An overall description of health and safety provisions in the plants surveyed according to their size is shown in Table V. There were obvious consistent differences in sanitary provisions, the availability of medical or nursing care, safety provisions, and the availability of environmental control measures between the small- and medium-size industries. Such provisions were more limited or almost absent in the small industries as compared to the medium-size ones, although the latter also suffer from generally unsatisfactory conditions. However, 45% of the medium-size industries had sanitary provisions such as showers and latrines, and overall cleanliness. Fifteen percent of them employed part-time physicians or nurses, and 42.5% had a part-time safety supervisor who was usually shared among several factories and 30% had introduced environmental control measures. In general their machinery was more modern and better guarded.

Observations on Table VI:

In Table VI an analysis of the conditions of work and the types of health hazards demonstrated a generally higher proportion of hazardous conditions in the small factories than in the medium-sized plants. The average number of health hazards per plant was 3.1 for the small-scale industries and 2.3 for the medium-size industries; a risk ratio of 1.34.

Observations on Table VII:

Table VII shows the distribution of the health hazards by type of industry. Most of the lead exposure was found as expected in printing and in wet battery manufacturing and to a lesser extent in workshops carrying out such operations as the repair of equipment containing lead. Irritant gases, fumes and smoke were encountered in practically all types of the industries surveyed; acids in battery operations; nitrogen and sulfur oxides, alkalis and acids in chemical industries; chlorine in bleaching operations in textiles; smoke from furnaces, welding operations and foundry works, including blacksmithis. Heat stress was mainly observed in the "workshops" and in ceramics and glass manufacturing. Most of the excessive noise occured in weaving and spinning and in machine operations in the "workshops". Inadequate lighting and accident potential were often found in the "workshops".

Answer 11b)

In Table II the largest proportion for the six "types" of manufacturing is "chemical" in the medium-sized plants; in Table VI, showing distribution of health hazards there are 21 out of 40 medium plants (52.5%) which suffered from "irritant gases and fumes"; possible cause/effect.

Answer 11c)

Yes, there is consistency in Table V showing lower provisions for health in the smaller plants by 25% in sanitation, 14% in absence of medical and/or nursing services, 21% in safety measures, and 10% in hazard control measures.

Answer 11d)

Chi X^2 test was applied for presence or absence of various health provisions in small and medium factories in Table V, which constitutes four two by two tables for each of

i) sanitation significantly lower at 1% level in small factories
$x^2 = 7.1245$
ii) medical or nursing provisions significantly lower at 5% level in small factories
$x^2 = 6.0124$
iii) safety provisions are significantly lower at 5% level in small factories
$x^2 = 4.9208$
iv) control measures not significantly different in small and medium industries
$x^2 = 1.3777$

PART 6

Answer 12

Expected

Industry	Health problems Yes	No
Small	158	168
Medium	546	577

$$x^2 = \frac{(197 - 158)^2}{158} + \frac{(507 - 546)^2}{546} + \frac{(129 - 168)^2}{168} + \frac{(616 - 577)^2}{577}$$

$$= 9.41 + 2.73 + 8.89 + 2.5$$

$$= 23.62$$

significant at 1% level or p 0.01.

Answer 13

Industry	Number of worker with illness	Number of illnesses	Average number of illnesses per worker affected
Small	197	343	1.74
Medium	507	556	1.10

$$\text{Risk ratio} = \frac{1.74}{1.10} = 1.60$$

Number of workers with illness = total workers examined = workers diagnosed with no illness.

Answer 14

The prevalence of different diseases among the workers examined in each type of industry is shown in Table X. Of the workers employed in printing and battery workshops, 37% showed manifestations of lead poisoning, as did 16% of the workers in ceramics and glass industries, probably due to absorption of lead used in glazing of ceramics and the addition of lead to glass in smelting processes. Occupational dermatitis was highest in the workshops where cutting-oils were frequently used. Upper-respiratory tract diseases and COPD occured in higher proportions among the textile workers, probably due to inhalation of vegetable dusts. Gastrointestinal, neurological, malnutrition and other health problems did not show marked differences in prevalence in any one single occupational group.

Answer 15

a) Yes, as follows:

  i) The study demonstrated that there were several probably serious health problems affecting the workers;
  ii) by the same methods used in studying small- and medium-sized industries, it was found that the small industries suffer the most and have very limited means for occupational health care;
  iii) the study demonstrated the need for occupational health personnel, equipment and laboratories;
  iv) the need for "on the spot" health supervision was demonstrated and was fulfilled by primary health care workers trained in occupational health;
  v) the need for regulatory action to control industrial health hazards was also demonstrated.

b) This is a cross-sectional study of health hazards and disease occurence (prevalence) in a representative sample of workplaces of different types and of the workers employed therein. The study takes place in a certain geographical location in a developing country which was keen to develop an occupational health programme.

As a follow-up to this study the following may be proposed:

i) to control the health hazards identified and treatment of the cases of illness;
ii) to widen the scope of the study;
iii) to re-examine the same workplaces and the workers using portable survey equipment and analytical diagnostic methods;
iv) to survey other occupations in other areas; and
v) to follow-up this population by monitoring after introducing central measures and appointing primary health care workers.

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